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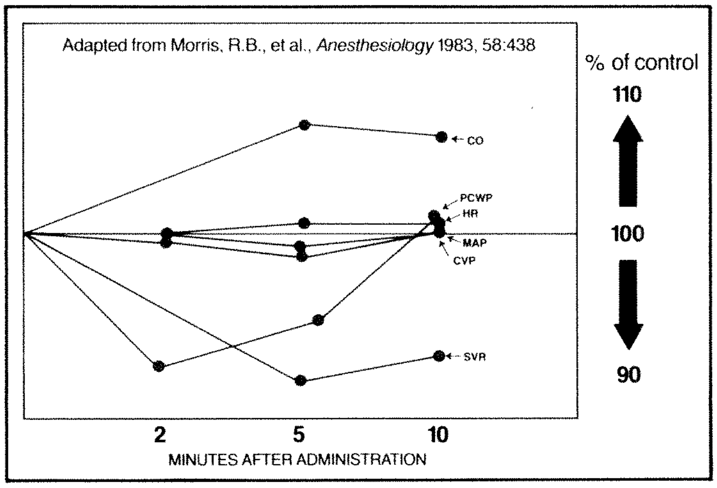
Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

1922

In neuromuscular blockade...

Closest to the ideal:



Adapted from Morris, R.B., et al., *Anesthesiology* 1983, 58:438

Free of clinically significant cardiovascular effects

NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.[1-3] This makes NORCURON unique among all neuromuscular blocking agents in clinical use.[4]

The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate[5]

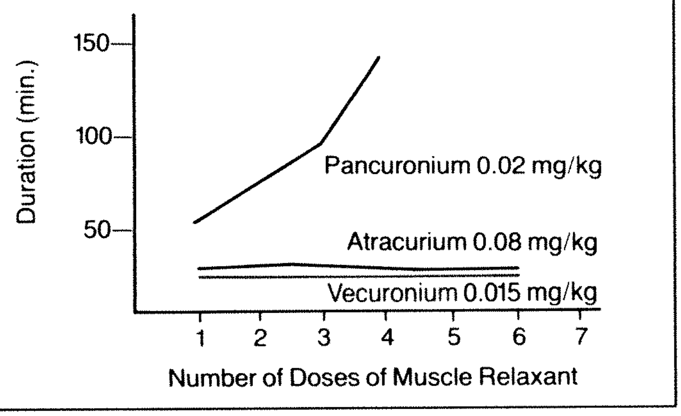
			Percent of Control		
Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
tubocurarine	0.5	1	318	78	116
metocurine	0.5	2	212	79	119
atracurium	0.6	3	192	80	108
vecuronium	0.1	1.7	117	100	99
vecuronium	0.2	3.5	87	99	102

Histamine release unlikely to occur

Histamine release has not been observed with NORCURON...as shown by preliminary clinical experience. In doses up to 3.5 times the ED_{95}, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.[5]

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.[5]

The Neuromuscular Effects of Maintenance Doses of Vecuronium, Atracurium and Pancuronium [6,7]



No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.[6,7]

CP24580

NORCURON®

(vecuronium bromide for injection)

Culo-H04007-10-P024580

Safety Index and Comparative Safety Ratios[8]

$$\text{Safety Index} = \frac{ED_{50}\ \text{autonomic inhibition}}{ED_{95}\ \text{neuromuscular blockade}}$$

Comparative Safety Ratios

For Vagolytic Effects		For CV/Histamine Related Effects	
gallamine	1:1	d-tubocurarine	1:1
pancuronium	3:1	metocurine	2:1
atracurium	25-30:1	atracurium	3:1
vecuronium	60:1	vecuronium	*

*cannot be calculated since it does not cause any CV or histamine related effects

Outstanding safety profile

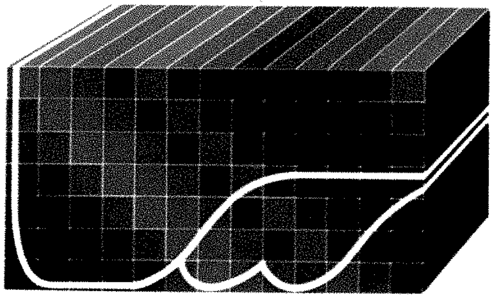
The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.[8]

The Safety Index is described as the ED_{50} for autonomic inhibition over the ED_{95} for neuromuscular blockade.[8]

A Comparison of Surgical Muscle Relaxants vs. The Ideal[4]
("+" signifies proximity to the ideal)

Characteristic	Vecuronium	Atracurium	Pancuronium	Succinylcholine	D-tubocurarine
Onset of Action	−	−	−	+	−
Histamine Release	+	−	+	+	−
Cardiovascular Side Effects	+	+/−	−	−	−
Duration of Action	+	+	−	+	−
Cumulative Effects	+	+	−	−	−
Rate of Recovery	+	+	−	+	−
Reversibility	+	+	+	−	+
Potency	+	+	+	−	−
Non-depolarizing	+	+	+	−	+
Metabolite Activity	+	+*	+	+	+

*Currently under evaluation.



NORCURON®
(vecuronium bromide for injection)

Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.[4]

Organon

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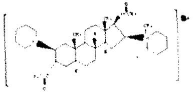
NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis (acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methyl-, bromide. The structural formula is:



Norcuron® is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes, subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron® (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron® (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide for injection).

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron® (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin, and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron® (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® (vecuronium bromide for injection) is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1 1/2 times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringers

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

SINGLE USE VIALS—Manufactured for ORGANON INC. By BEN VENUE LABORATORIES, INC., Bedford, Ohio 44146

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Anesthesia and Analgesia

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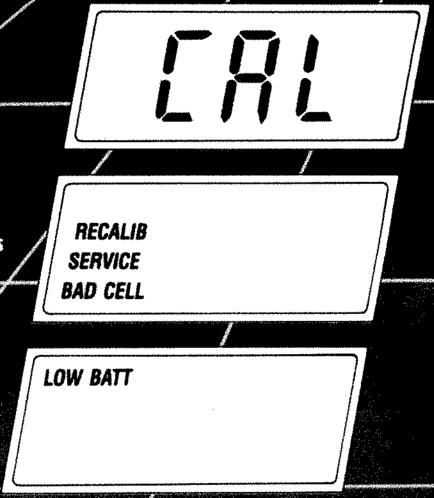

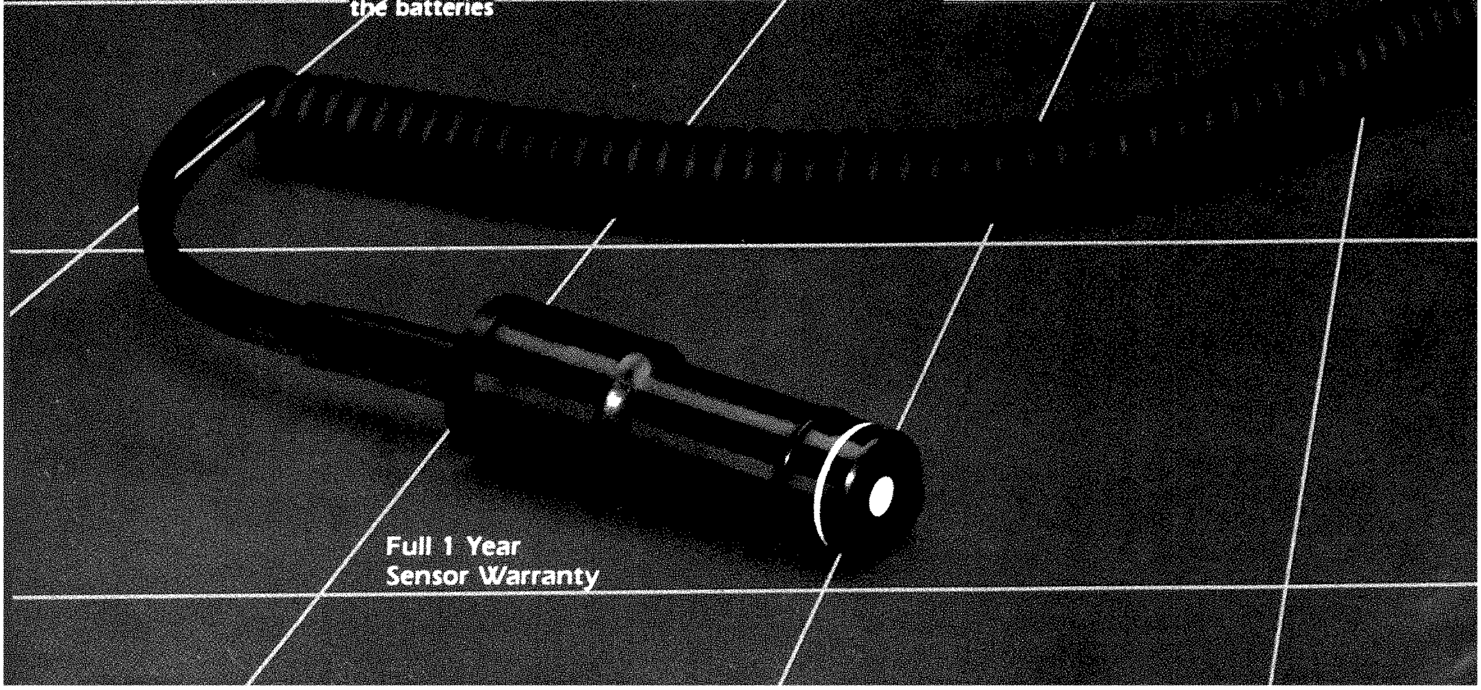

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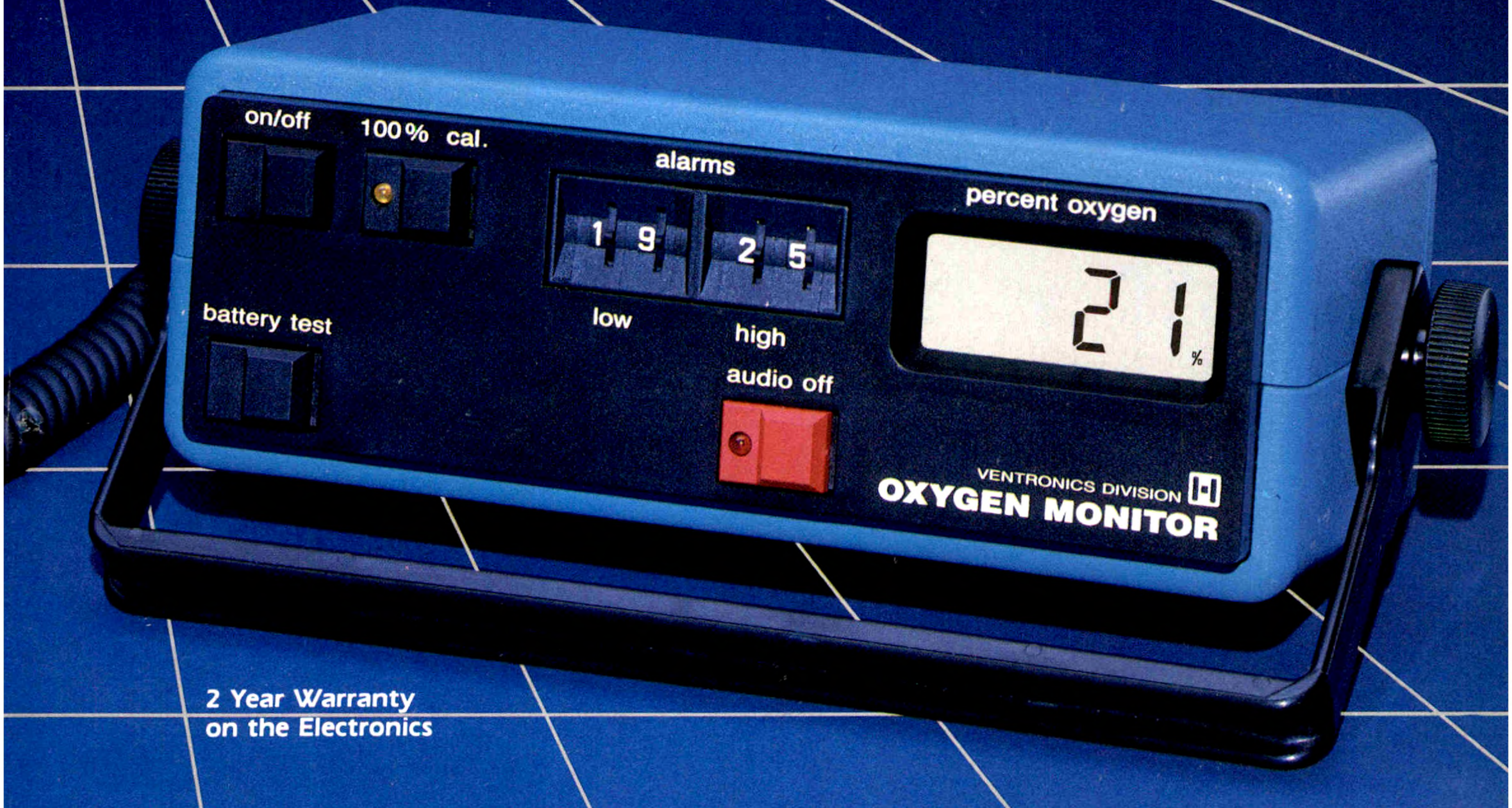

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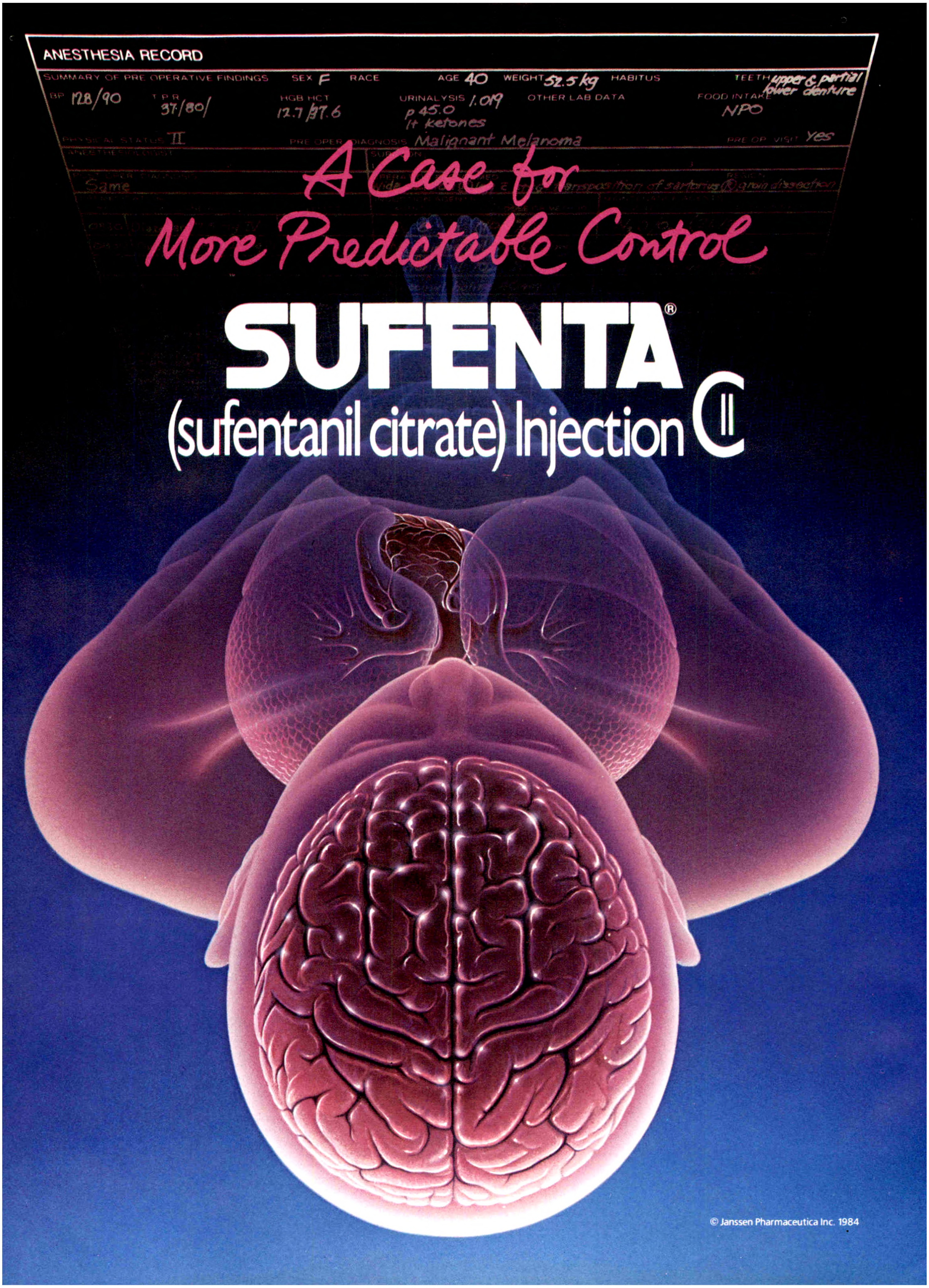

ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS SEX F RACE AGE 40 WEIGHT 52.5 kg HABITUS TEETH upper & partial lower denture

BP 128/90 T P R 37/80/ HGB HCT 12.7/37.6 URINALYSIS 1.019 p 45.0 1+ ketones OTHER LAB DATA FOOD INTAKE NPO

PHYSICAL STATUS II PRE OPER DIAGNOSIS Malignant Melanoma PRE OP VISIT Yes

ANESTHESIOLOGIST SURGEON

POST OPER DIAGNOSIS Same OPERATION PERFORMED Wide [illegible] c [illegible] transposition of sartorius Ⓡ groin dissection REGION

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...More Predictable Control from Induction through Recovery

COMPARED WITH ISOFLURANE*[1,2]

- Superior hemodynamic stability
- Shorter recovery times
- Better maintenance of postoperative analgesia
- Lower total cost per procedure

*In a comparative study[1,2] of patients undergoing major orthopedic surgery who received either SUFENTA-N_2O (n=10) or isoflurane-N_2O (n=10).

1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

COMPARED WITH FENTANYL[3,4]

- Smoother, more rapid induction
- Smoother, more stable intraoperative course
- Faster, more comfortable recovery
- More effective blocking of surgical stress response
- Superior hemodynamic stability
- Smaller volume of injection
- Lower total cost per procedure

3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.
4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

For complete Product Information, please see next page. JPI-514

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PHARMACEUTICA

SUFENTA®
(sufentanil citrate) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be ⅕-⅐ those of fentanyl on a mg/kg basis.) At doses of up to 8 μg/kg, SUFENTA provides profound analgesia; at doses ≥8 μg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 μg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 μg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 μg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 μg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 μg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 μg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 μg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 μg/kg in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).
Other adverse reactions with a reported incidence of less than 1% were:
Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 μg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 μg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 μg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 μg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
1-2 μg/kg: administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 μg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
2-8 μg/kg: administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
8-30 μg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 μg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 μg/kg, catecholamine release is attenuated. Dosages of 25-30 μg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 μg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 μg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 μg/ml, 5 ml ampoules in packages of 10

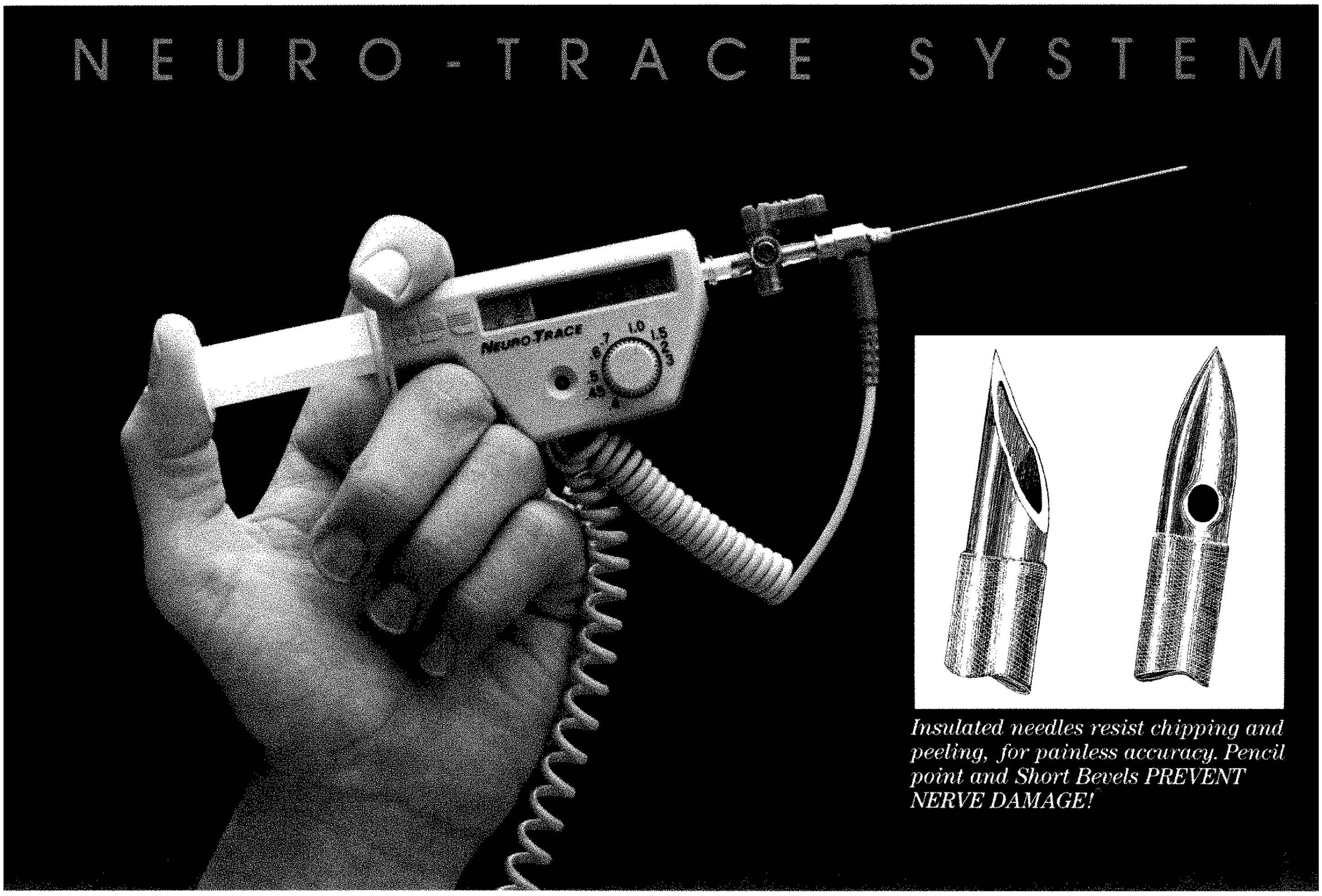
Protect from light. Store at room temperature.

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854

7618500

U.S. Patent No. 3,998,834
May 1984

WHY RISK NERVE DAMAGE?



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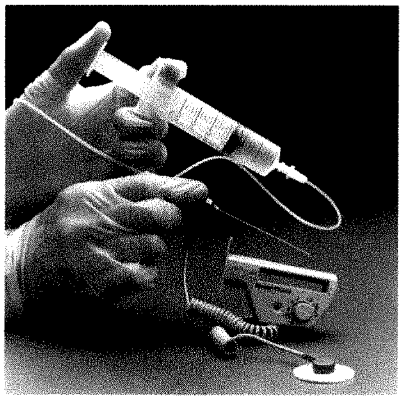

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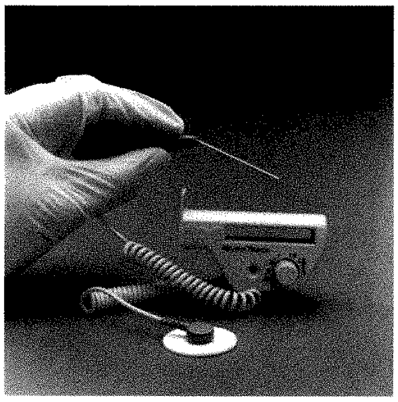

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Nerve Locator.
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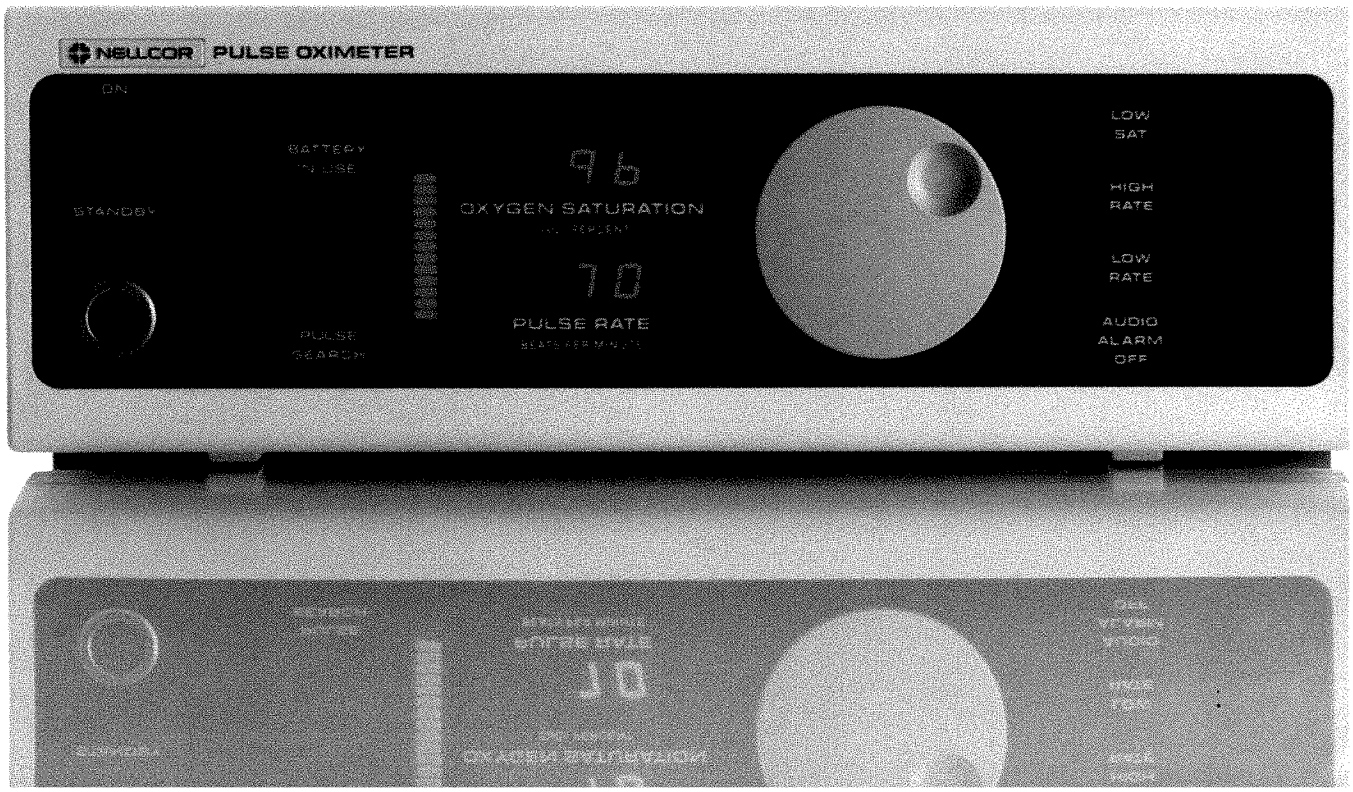
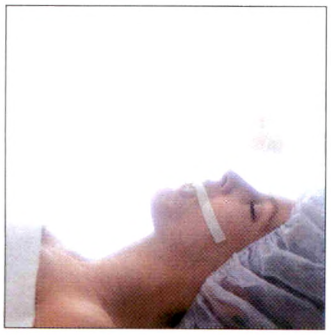
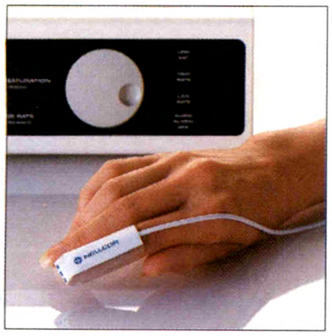
> *"Hypoxia is a major cause of morbidity and mortality during anesthesia."*[1]

PUT AN END TO HYPOXEMIA COMPLICATIONS.

> *"...current methods of cardiac monitoring may detect cardiac dysfunction too late to permit brain survival."*[2]
>
> *"There is no question that routine, continuous oximetry is an additional technology which could essentially eliminate this very expensive source of anesthesia malpractice claims."*[3]
>
> *"...our most pressing needs are for monitoring... the state of tissue oxygenation..."*[2]
>
> *"Changes in oxygen saturation occur frequently during anesthesia regardless of the skill and experience of the anesthetist... Continuous oximetry provides for early recognition and timely treatment of desaturation well before the onset of cyanosis, a* sine qua non *of quality patient care."*[4]







THE NELLCOR PULSE OXIMETER.® THE BEST INSURANCE AGAINST UNDETECTED HYPOXEMIA.

The Nellcor Pulse Oximeter. By continuously monitoring patients' arterial hemoglobin oxygen saturation levels, it detects hypoxemia before it can lead to serious medical problems.

A precalibrated, comfortable photosensor is simply placed on the patient and the monitor turned on.

Everything you need is right at hand. Immediately. Continuously. Accurately. And non-invasively.

With each heartbeat, there are real time measurements of arterial saturation, pulse rate and pulse amplitude.

And it doesn't have to be watched because there is an audible beep with each heartbeat that changes pitch to reflect any change in oxygen saturation levels.

Plus, alarms warn instantly if pulse rate or saturation fall outside of preset limits.

Early warning for instant treatment before damage can occur.

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The Nellcor Pulse Oximeter. The best insurance against undetected hypoxemia.

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Hayward, California 94545
415/887-5858

[1] Flynn M: Hypoxemia Detection During Pediatric Endoscopy. Presented at The American Academy of Pediatrics, 1983, pp 1-2.

[2] Davis DA: An Analysis of Anesthetic Mishaps from Medical Liability Claims, in Pierce EC Jr, Cooper JB (eds): *Analysis of Anesthetic Mishaps*. International Anesthesiology Clinics, Boston, Little, Brown and Company, 1984, Vol 22, No 2, pp 31-42.

[3] Rubsamen DS (ed): Professional Liability Newsletter, 1984, Vol 15, No 6.

[4] Whitcher C, New W Jr, Bacon B: Perianesthetic oxygen saturation vs. skill of the anesthetist. Anesthesiology 57: 1982. Suppl to abstract for American Society of Anesthesiologists, October 18, 1982.

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NC003-1184

INVASIVE PROCEDURES...

On the eve of surgery, anxiety can reach excessive levels. At such times, oral Valium (diazepam/Roche) is often especially useful. Its dependable calming action rapidly relieves anxiety—helps assure a more tranquil preoperative night. And Valium is well tolerated by most patients: side effects more serious than fatigue, drowsiness or ataxia are rare.

the night before

Oral
VALIUM® Ⓘⓥ
diazepam/Roche

scored tablets

2 mg 5 mg 10 mg

Note our distinctive look

to control mounting anxiety

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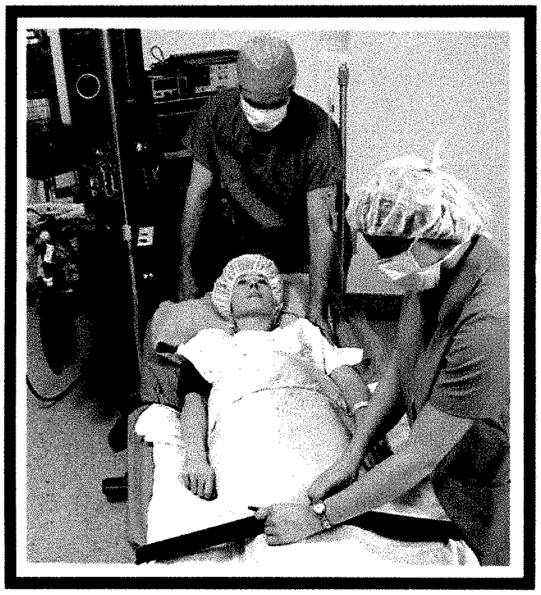
ROCHE®

PERVASIVE ANXIETY

With Injectable Valium (diazepam/Roche) I.V., the course of action is predictable: its calming effect usually occurs within minutes,[1,2] bringing acute anxiety and apprehension under rapid control. Most patients are relaxed but still able to follow simple instructions. Anterograde amnesia also begins in minutes, rarely persists beyond an hour.[2-6] Although Injectable Valium has an excellent safety record, resuscitative facilities should be readily available. Narcotic dosage should be reduced by at least one-third. For warnings and precautions, see complete product information.

minutes before

Injectable
VALIUM® I.V.
diazepam/Roche Ⓒ



to control anxiety and diminish recall

See next page for references and a summary of product information.

References: **1.** Diazepam and lorazepam in anaesthesia. *Drug Ther Bull 17*(5):19-20, Mar 2, 1979. **2.** Conner JT, *et al: J Clin Pharmacol 18:*285-292, May-Jun 1978. **3.** George KA, Dundee JW: *Br J Clin Pharmacol 4:*45-50, Feb 1977. **4.** Dundee JW, Pandit SK: *Br J Pharmacol 44:*140-144, Jan 1972. **5.** Dundee JW, *et al: Br J Anaesth 51:*439-446, May 1979. **6.** Gregg JM, Ryan DE, Levin KH: *J Oral Surg 32:*651-664, Sep 1974.

Injectable Valium® (diazepam/Roche) Ⓒ
Valium® (diazepam/Roche) Ⓒ

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications: Tablets in children under 6 months of age; known hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.,* operating machinery, driving). Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of predisposition to habituation/dependence.

> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

ORAL: Advise patients against simultaneous ingestion of alcohol and other CNS depressants.

Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least ⅓, administer in small increments.

Injectable Valium® (diazepam/Roche)
Valium® (diazepam/Roche)

Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs.

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status. Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium, *i.e.,* phenothiazines, narcotics, barbiturates, MAO inhibitors and antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed and tolerated).

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

INJECTABLE: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium therapy and are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension. Dialysis is of limited value.

How Supplied

ORAL: Round, scored tablets* with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500; Prescription Paks of 50, available in trays of 10. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

INJECTABLE:† Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10.

*Supplied by Roche Products Inc., Manati, Puerto Rico 00701
†Manufactured by Hoffmann-La Roche Inc., distributed by Roche Products Inc.

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A first in selective spinal analgesia:

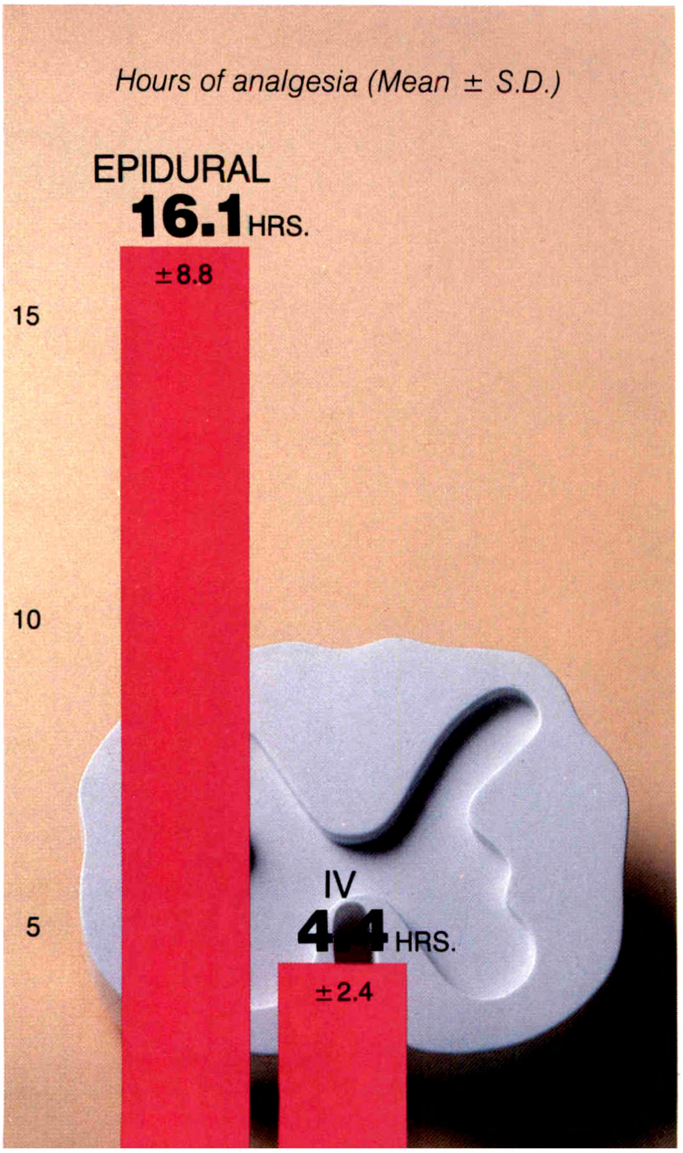
The discovery of opiate receptors
in the dorsal horn of the spinal cord
has created exciting new options
in pain management.

A·H·ROBINS

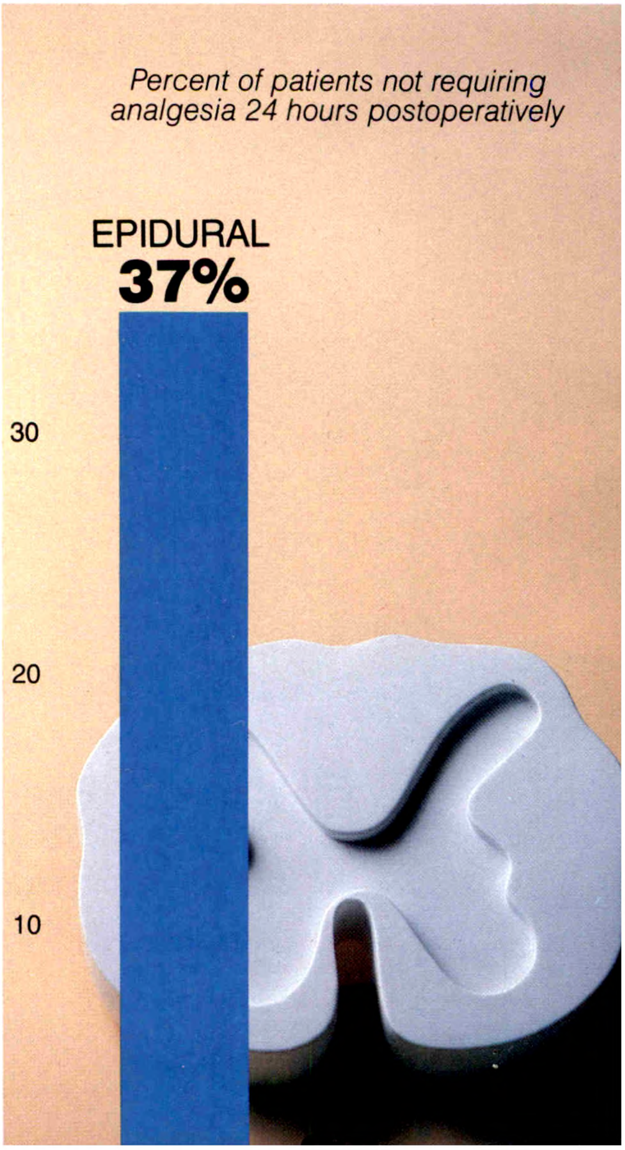
Prolonged postoperative analgesi with a single epidural injection . . .

DURAMORPH® PF PROVIDES SUPERIOR ANALGESIA WHEN COMPARED W

DURATION OF PAIN RELIEF IS NEARLY QUADRUPLED



POSTOPERATIVE ANALGESIA OFTEN LASTS UP TO 24 HOURS



PRESERVATIVE-FREE

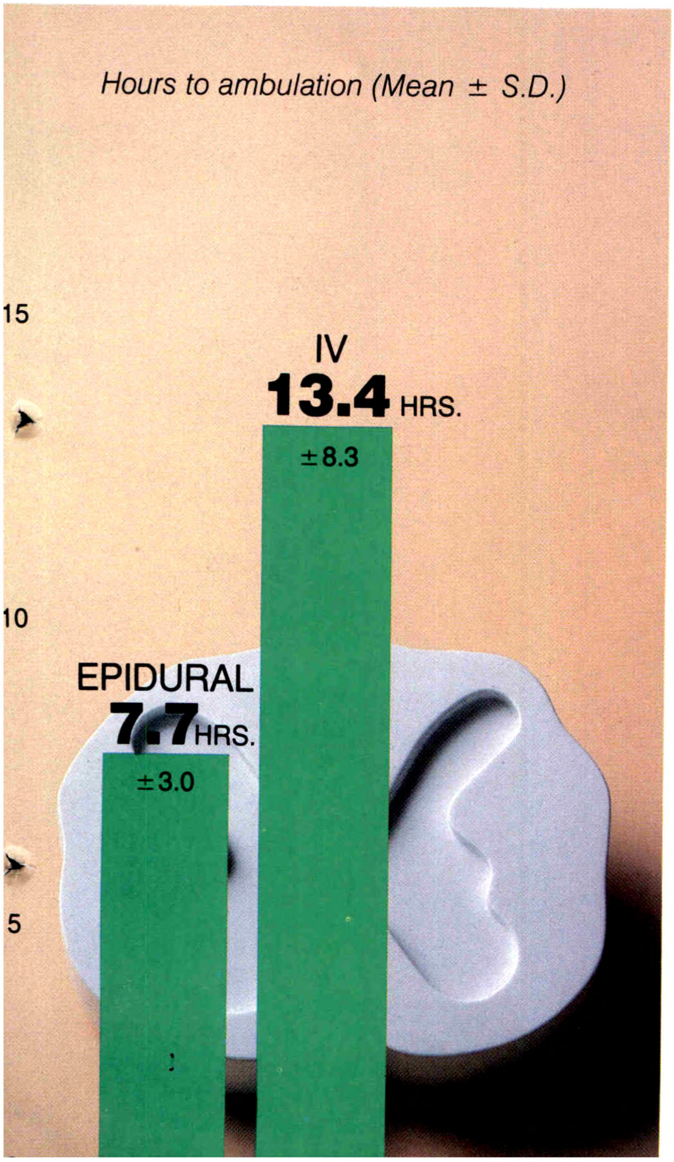
Duramorph® PF

(morphine sulfate injection, USP) C II

CONVENTIONAL NARCOTIC ADMINISTRATION:

POSTOPERATIVE PATIENTS MAY BE AMBULATORY IN HALF THE TIME

*Charts depict the results of a double-blind study comparing the analgesic efficacy of 5 mg epidural morphine (N = 19) with that of 5 mg intravenous (IV) morphine (N = 19) following cesarean section.**



- **Virtually no sedation or loss of motor function**
  DURAMORPH® PF administered epidurally relieves pain with little effect on sensory, motor or sympathetic function. Patients are alert, cooperative and able to move about without discomfort.
- **No potentially neurotoxic additives**
  Unlike other morphine preparations, DURAMORPH® PF contains no bisulfites, phenols, chelating agents, paraben preservatives, or benzyl alcohol that may cause neurotoxicity when administered epidurally.
- **Low incidence of respiratory depression**
  Delayed respiratory depression has been reported. Patients should be monitored closely for 24 hours postoperatively after each dose. If respiratory depression should occur, it can be reversed readily with naloxone, without affecting the quality of analgesia.

*Cohen SE, Woods WA: Anesthesiology 58:500, 1983

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PRESERVATIVE-FREE

Duramorph PF®

(morphine sulfate injection, USP) CII

DESCRIPTION
Preservative-free DURAMORPH® PF (Morphine Sulfate Injection, USP) is a sterile, pyrogen-free, isobaric solution free of antioxidants, preservatives or other potentially neurotoxic additives, and is intended for intravenous, epidural or intrathecal administration as a narcotic analgesic. Each milliliter contains morphine sulfate 0.5 mg or 1 mg (Warning: May Be Habit Forming) and sodium chloride 9 mg in Water for Injection. pH range is 2.5-6.0. Ampuls are sealed under nitrogen. Each Dosette® ampul is intended for SINGLE USE ONLY. Discard any unused portion. DO NOT AUTOCLAVE.

INDICATIONS AND USAGE
Preservative-free DURAMORPH® PF is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

CONTRAINDICATIONS
DURAMORPH® PF is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

WARNINGS
DURAMORPH® PF administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.

FACILITIES WHERE DURAMORPH® PF IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.

SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.

Morphine sulfate may be habit forming. (See Drug Abuse and Dependence section.)

PRECAUTIONS

GENERAL
Preservative-free DURAMORPH® PF (Morphine Sulfate Injection, USP) should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial/intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis).

Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

It is recommended that administration of DURAMORPH® PF by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to risks inherent in urethral catheterization, e.g., sepsis, when epidural or intrathecal administration is considered, especially in the perioperative period.

Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

DRUG INTERACTIONS
Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY
Teratogenic effects—Pregnancy Category C. Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.

Nonteratogenic effects. Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

LABOR AND DELIVERY
Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

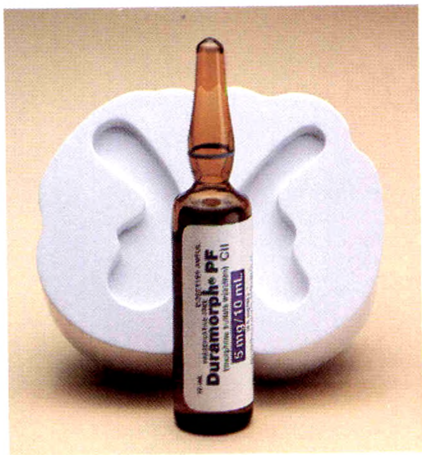
Epidurally and intrathecally administered morphine readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that *epidural* administration has little or no effect on the relief of labor pain.

However, studies have suggested that in most cases 0.2 to 1 mg of morphine *intrathecally* provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr, for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

NURSING MOTHERS
Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

PEDIATRIC USE
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The most serious side effect is respiratory depression. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (See Warnings and Overdosage sections). Even without clinical evidence of ventilatory inadequacy, a diminished CO_2 ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.



While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.

Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10-20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see Precautions). Pruritus, nausea/vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).

Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see Drug Abuse and Dependence section).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as uticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: Morphine sulfate is a Schedule II substance under the Drug Enforcement Administration classification.

Abuse: Morphine has recognized abuse potential.

Dependence: Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Nonteratogenic effects under Pregnancy.)

OVERDOSAGE
Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, simultaneously with respiratory resuscitation. *As the duration o effect of naloxone is considerably shorter than that of epidural o intrathecal morphine, repeated administration may be necessary.* Patients should be closely observed for evidence of renarcotization. *Note: Respiratory depression may be delayed in onset up to 2 hours* following epidural or intrathecal administration. In painfu conditions, reversal of narcotic effect may result in acute onset o pain and release of catecholamines. Careful administration o naloxone may permit reversal of side effects without affectin analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

HOW SUPPLIED
Amber Dosette® ampuls for intravenous, epidural and intratheca administration.

5 mg/10 mL (0.5 mg/mL) packaged in 10s (NDC 0641-1113-33

10 mg/10 mL (1 mg/1 mL) packaged in 10s (NDC 0641-1115-33

Revised September 198

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IARS MEMBERSHIP

P24580

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS Research Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

. . . . MEMBERSHIP CATEGORIES . . . .

MEMBERSHIP: Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

Annual Dues for Members and Associate Members: $45.00 U.S.; $55.00 foreign. These memberships are entered on a calendar year basis only.

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians.

Annual Dues for Educational Members: One-half of member rate. These memberships are entered in January or July and are for 2- or 3-year periods only. Applications, certified by program directors, must accompany check to cover full membership period.

- -

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

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Please print clearly: ____
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

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Street Address
City, State, Zip Code (country)

for prolonged procedures:

Mastectomy

Coronary Bypass

Hysterectomy

prolonged action can be a plus.

Premedication with Ativan® (lorazepam) Injection may well be the most logical choice for longer surgical procedures where extended sedation and/or lack of recall are especially desirable.

A single injection of Ativan Injection provides dependable sedation for 6-8 hours. When surgery runs longer than anticipated, or unexpected delays occur, repeated injections may not be required.

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Hip Replacement

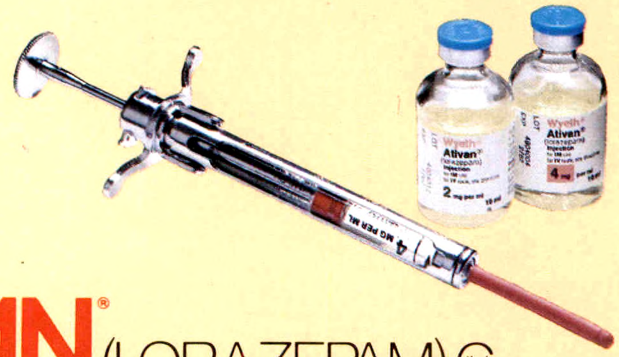
Cholecystectomy

Knee Surgery

Head and Neck

Administered as recommended, Ativan Injection allays preoperative apprehension, relieves anxiety, leaves patients calm but cooperative and diminishes recall of events surrounding surgery. There is little, if any, IV irritation at proper dilution, and only minimal effects on blood pressure, pulse or respiratory rate.

The dosage of Ativan® (lorazepam) Injection should be individualized for each patient. For those in whom reduced recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom lack of recall is not desired, and for the elderly or debilitated, the dose should be reduced.



ATIVAN® (LORAZEPAM) Ⓒ
INJECTION IM or IV

See important information on following page.

Wyeth Laboratories
Philadelphia, PA 19101

ATIVAN® (LORAZEPAM) ⒸIV
INJECTION IM or IV

DESCRIPTION: Ativan* (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

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Soothing news for busy anesthesiologists

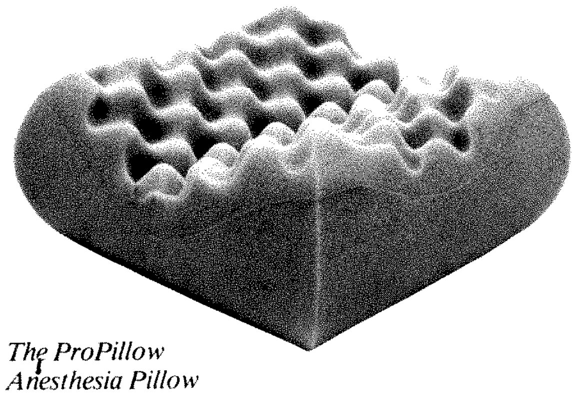
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

The ProPillow takes the pressure off

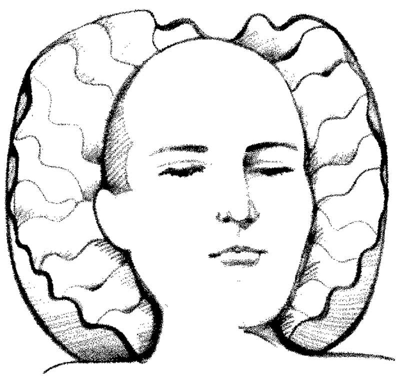
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



The ProPillow
Anesthesia Pillow

The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.

An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

And the price is right

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California**, or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

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The pioneers of neurological surgery were more than ordinary men and women: they were risk-takers of great determination and strength with universal human weaknesses. Their successes and failures constitute the history of neurological surgery.

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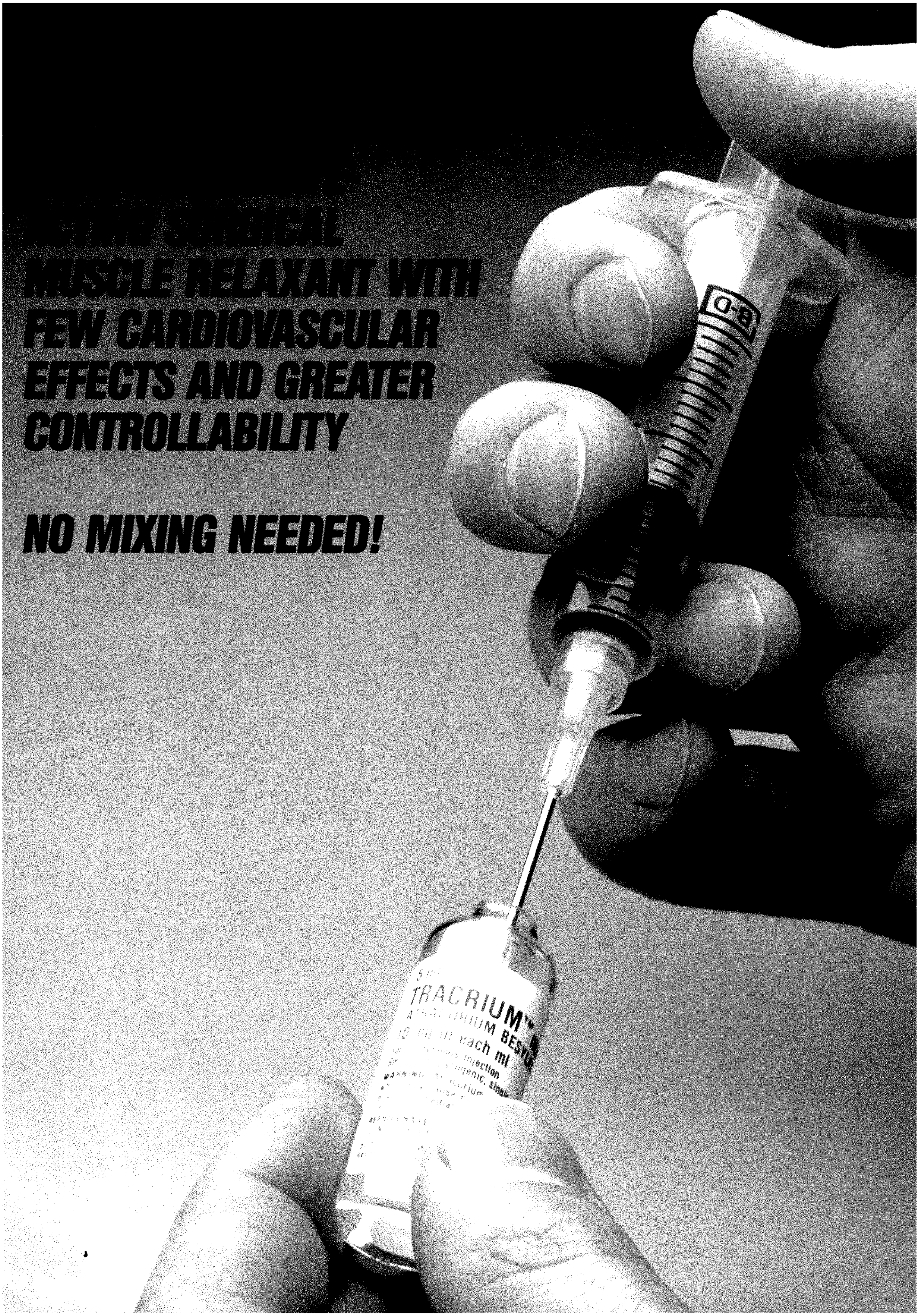
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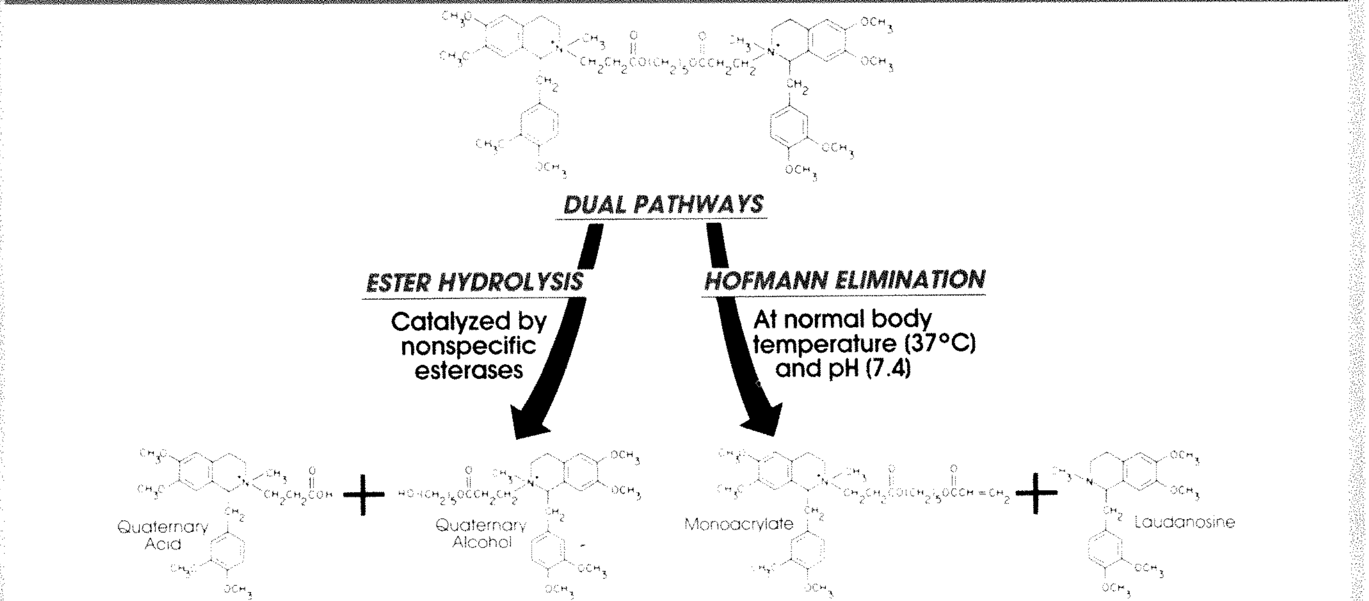


☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH

2 Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required

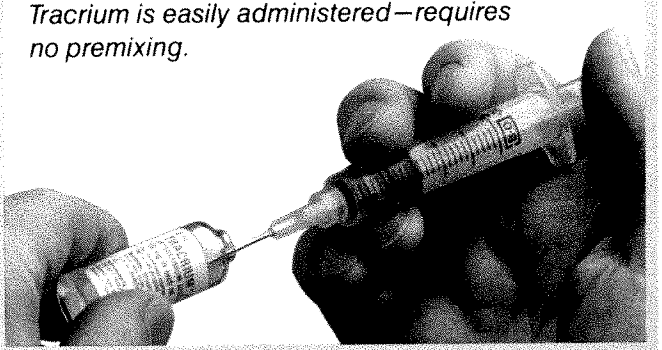
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

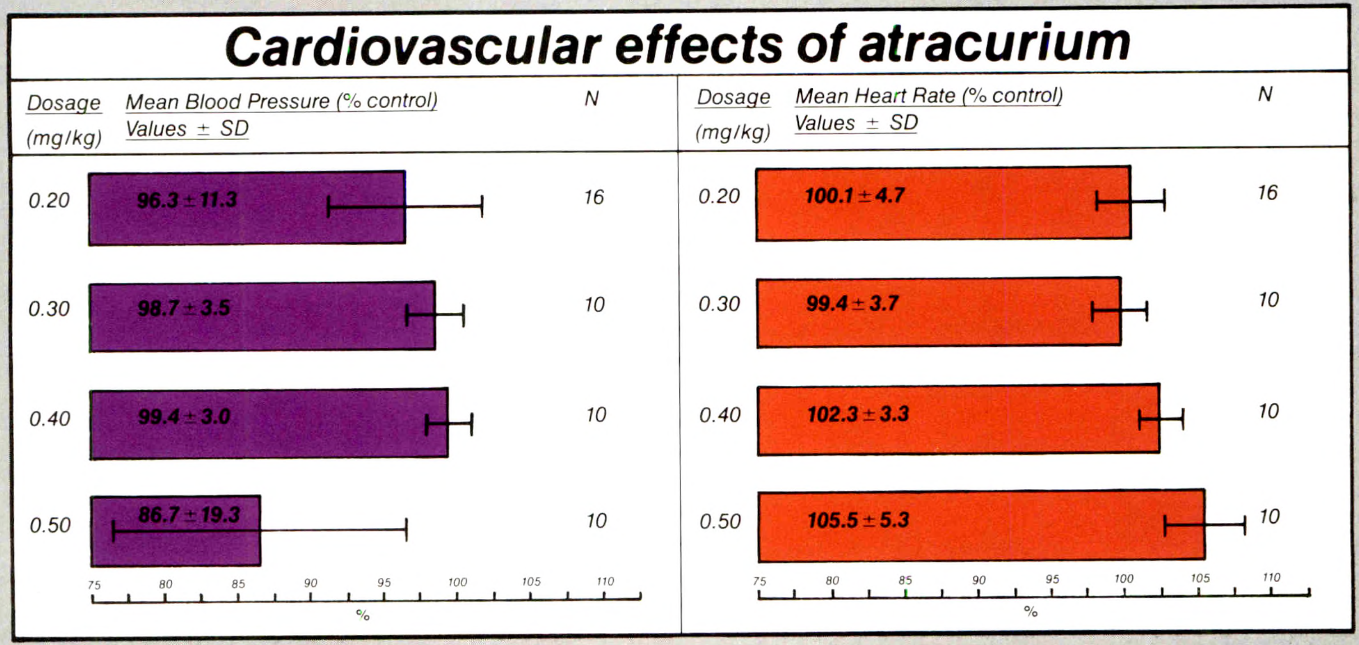
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ *Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.*



Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ *Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

☐ *Once recovery begins, it is relatively rapid and independent of dose*

☐ *This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

Minimal Histamine Release

☐ *Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

☐ *Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium*[4]

☐ *The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

Please see brief summary of prescribing information on the following page.

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TRACRIUM® INJECTION
(atracurium besylate)

TRACRIUM® INJECTION
(atracurium besylate)

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3. mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).
Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

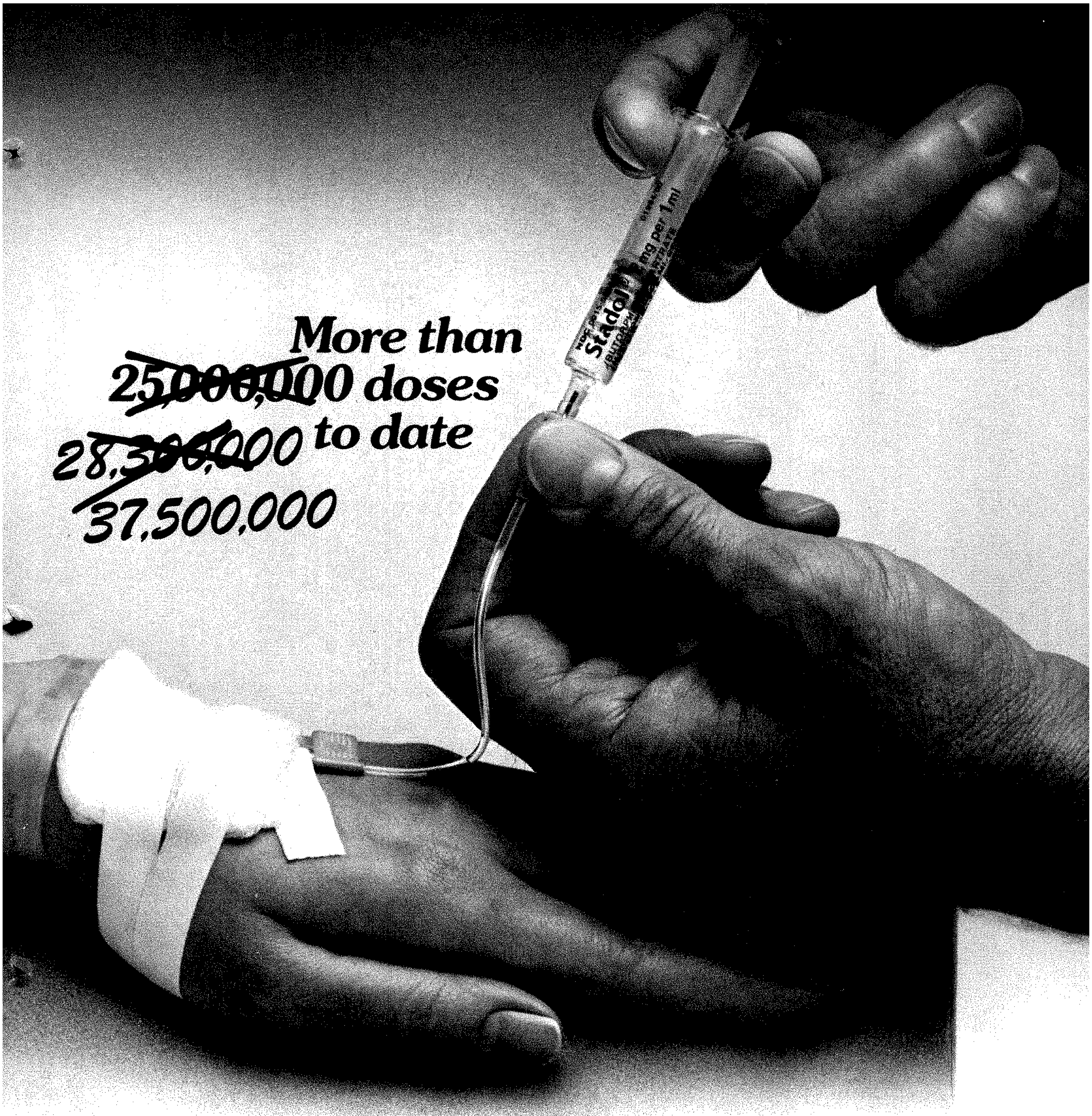
U.S. Patent No. 4179507

Printed in U.S.A.

84-TRA-4

TRACRIUM® INJECTION
(atracurium besylate)

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709



HOSPITAL-PROVEN

Stadol® IM IV
(butorphanol tartrate)

BRISTOL™

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Division of Bristol-Myers Company
Syracuse, New York 13221-4755

The premedication that well into the

Before Surgery

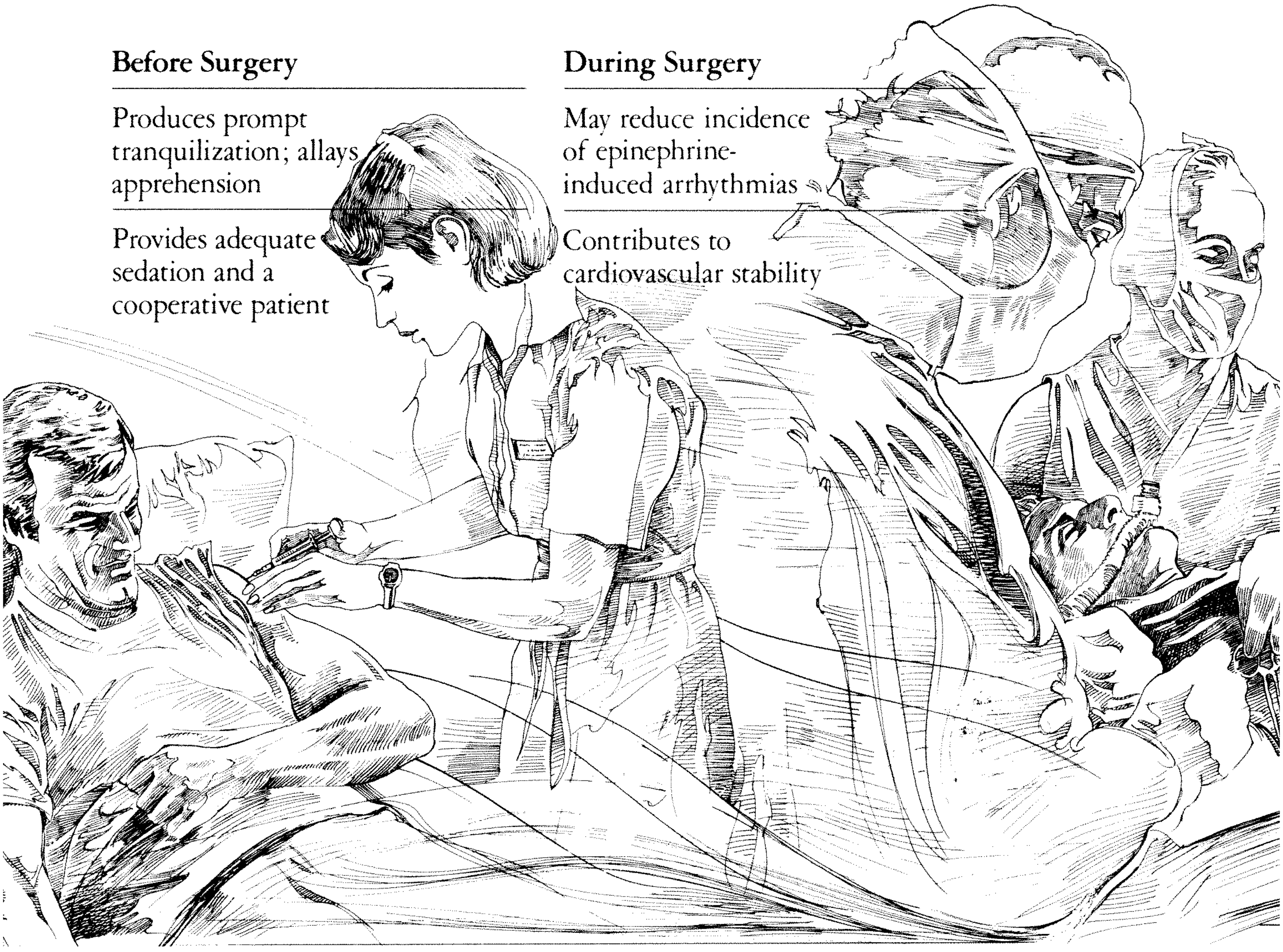
Produces prompt tranquilization; allays apprehension

Provides adequate sedation and a cooperative patient

During Surgery

May reduce incidence of epinephrine-induced arrhythmias

Contributes to cardiovascular stability



Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:
2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol . . . . 2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol . . . . 2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

goes on helping... postoperative period

After Surgery

Exerts potent antiemetic effect

Reduces need for postoperative narcotics

Inapsine® (droperidol) Injection

The premedication that does more than premedicate

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur.

Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: 2 ml. and 5 ml. ampoules—packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980
*See full prescribing information for complete description.
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JANSSEN
PHARMACEUTICA

JPI-342

Janssen Pharmaceutica Inc. 501 George St., New Brunswick, N.J. 08903

Marcaine® Spinal

bupivacaine HCl, USP, 0.75%
with dextrose, USP, 8.25% injection

PLEASE CONSULT FULL PRESCRIBING INFORMATION: A SUMMARY FOLLOWS:

CONTRAINDICATIONS: MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type. The following conditions preclude the use of spinal anesthesia: (1) Severe hemorrhage, severe hypotension, or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output; (2) Local infection at the site of proposed lumbar puncture; (3) Septicemia.

WARNINGS: LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE AVAILABILITY** OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid while performing spinal anesthesia indicates entry into the subarachnoid space. Aspiration should be performed before the anesthetic is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because severe, persistent hypertension may occur. MARCAINE solutions containing a vasoconstrictor such as epinephrine should be used cautiously in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Administration of MARCAINE to patients younger than 18 years is not recommended, nor is the mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE because of insufficient data on the clinical use of such mixtures.

PRECAUTIONS: General: The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patients should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anesthetic injection should be constantly and carefully monitored. Restlessness, anxiety, incoherent speech, light-headedness, numbness, and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used cautiously in patients with severe disturbances of cardiac rhythm, shock or heart block.

Sympathetic blockade during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should also be carefully monitored because it is not always controllable in spinal techniques.

Because the liver metabolizes amide-type local anesthetics such as MARCAINE, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used cautiously in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than those in other major blocks; most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be considered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It is not known whether amide-type local anesthetics trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome depends on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending on the physician's evaluation of the situation and ability to deal with possible complications or complaints: (1) Preexisting diseases of the central nervous system, such as those resulting from pernicious anemia, poliomyelitis, syphilis, tumor; (2) Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage; (3) Chronic backache and preoperative headache; (4) Hypotension and hypertension; (5) Technical problems (persistent paresthesias or bloody tap); (6) Arthritis or spinal deformity; (7) Extremes of age; (8) Psychosis or other causes of poor cooperation by the patient.

Information for Patients: Patients should be informed that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

Clinically Significant Drug Interactions: Local anesthetic solutions containing epinephrine or norepinephrine administered to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided but, when necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals of most local anesthetics including bupivacaine to evaluate carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic, or mutagenic or that it impairs fertility.

Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of bupivacaine's effect on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See **Labor and Delivery.**)

Labor and Delivery: Spinal anesthesia has a *recognized* use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Regional anesthesia has produced maternal hypotension. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may result in diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

Cardiac arrest has been reported during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The MARCAINE hydrochloride package insert for epidural, nerve block, etc, discusses this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for obstetrical spinal anesthesia. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

Nursing Mothers: It is not known whether local anesthetic drugs are excreted in human milk; therefore, caution should be exercised when local anesthetics are administered to a nursing woman.

Pediatric Use: Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

ADVERSE REACTIONS: Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences following spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Respiratory System: Respiratory paralysis or underventilation may result from upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation may contribute to underventilation. This will usually occur within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, intercurrent drug use, and surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood and interstitial fluid volumes, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injections may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

Neurologic: Adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also depend on the particular drug used, the route of administration and the physical status of the patient. Many effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus; arachnoiditis; slowing of labor, increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; fecal and urinary incontinence.

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions include urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

Other: Nausea and vomiting may occur during spinal anesthesia.

OVERDOSAGE: Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone or contributory mechanical obstruction of venous return.

Management of Local Anesthetic Emergencies: The first consideration is prevention through careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. Administer oxygen at the first sign of change.

The first step in managing systemic toxic reactions, as well as underventilation or apnea due to a high or total spinal is to ***immediately*** *establish and maintain a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after instituting these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation.

Hypotension due to sympathetic relaxation may be managed with intravenous fluids, in an attempt to relieve mechanical obstruction of venous return or by using vasopressors and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the physician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in maintaining a patent airway or if prolonged ventilatory (assisted or controlled) support is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

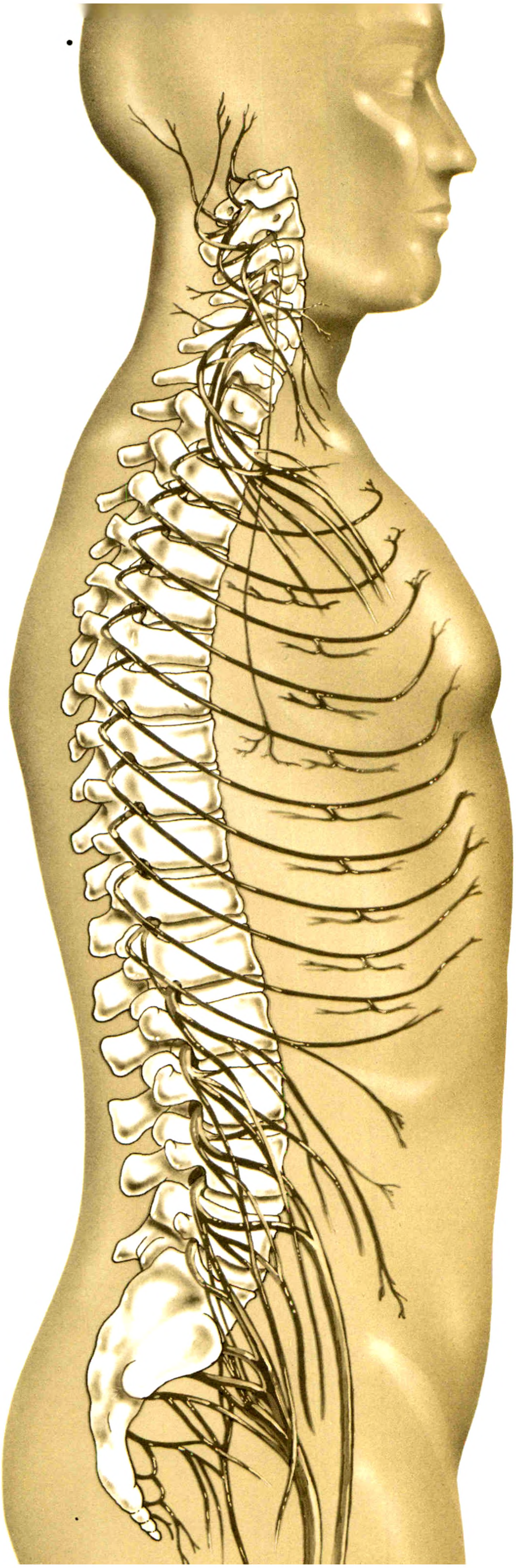
The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD_{50} in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

Composition of MARCAINE Spinal Solutions: Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C, and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

Winthrop-Breon

WINTHROP-BREON LABORATORIES
Division of Sterling Drug Inc.
New York, NY 10016



Introducing a reliable anesthetic for spinal anesthesia

Few spinal anesthetic failures

New Marcaine® Spinal offers the advantage of dependable and profound anesthesia for a wide variety of surgical and obstetrical procedures. **MARCAINE** Spinal in a dose of 7.5 mg had only one anesthetic failure in 121 patients.*[1]

"...reliable local anesthetic solution for spinal anesthesia."[1]

- Rapid onset—within one minute
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Reference:
1. Moore DC: Spinal anesthesia: Bupivacaine compared with tetracaine. *Anesth Analg* 1980; 59:743-750.

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I.A.R.S. 59th CONGRESS—MARCH 9–13, 1985
ADAM'S MARK HOTEL—HOUSTON, TEXAS

SCIENTIFIC PROGRAM SUMMARY: 26 Review Course Lectures; 2 Panel Presentations; 8 Theme Luncheons; 114 Scientific Papers; Exhibits;

T. H. Seldon Distinguished Lecture: *"Standards for Excellence"*—M. T. Jenkins, M.D.

MEETING SCHEDULE:

Saturday, March 9:	Registration—1 to 7 p.m. (Continues throughout meeting)
Sunday, March 10:	
8–5 PM	Review Course Lectures
9–12 PM	Panel—"Cardiac Anesthesia—Case Discussions"
2–5 PM	Panel—"Impact of Legislation and Regulation on Economics in Anesthesiology"
12–5 PM	Scientific and Technical Exhibits Open
6–7 PM	Complimentary Informal Reception
Monday, March 11:	
8–12 PM	Three Concurrent Sessions: Room 1—Review Course Lectures; Rooms 2 and 3—Scientific Papers
1:15–2 PM	T. H. SELDON DISTINGUISHED LECTURE
2–5 PM	Three Concurrent Sessions (as above)
9–3 PM	Scientific and Technical Exhibits
Tuesday, March 12:	
8–5 PM	Three Concurrent Sessions (as above)
12–2 PM	Four Concurrent Theme Luncheon Sessions
12–5 PM	NASA Tour
9–1 PM	Scientific and Technical Exhibits (Final Day of Exhibits)
Wednesday, March 13:	
8–5 PM	Three Concurrent Sessions (as above)
12–2 PM	Four Concurrent Theme Luncheon Sessions

REGISTRATION FEES: Amounts shown include choice of all sessions except Theme Luncheons ($12 each) and NASA Tour ($19.50 including box lunch)

I.A.R.S. Members and Associate Members:	$150—pre-registration ($175 on site)
I.A.R.S. Educational Members:	NO FEE
Non-I.A.R.S. Members:	$175—pre-registration ($200 on site)
Non-member Residents, Students:	$25 (with certification from Program Director)

CME CREDITS: As an organization accredited for continuing medical education by ACCME, the I.A.R.S. designates this activity as Category 1 of the Physicians Recognition Award. One credit hour may be claimed for each hour of participation, up to a maximum of 31 hours. AANA—Prior approval pending for 31 AANA credits.

PRE-REGISTRATION MAILING

The preliminary program showing daily schedule; hotel card; Delta Airlines special fare information for U.S. registrants; and schedule of social activities for guests and registrants will be mailed in mid-December to all I.A.R.S. members. Enrollment forms for Theme Luncheons NASA Tour and Social Program will be sent only to those who pre-register for the meeting, and will be assigned on a first-come basis. Non-members may receive material by writing to:

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Prolonged Hyporesponsiveness of Vascular Smooth Muscle Contraction after Halothane Anesthesia in Rabbits

Christian K. Spiss, MD, Christopher M. Smith, MSc, Gozoh Tsujimoto, MD,
Brian B. Hoffman, MD, and Mervyn Maze, MD

SPISS CK, SMITH CM, TSUJIMOTO G, HOFFMAN BB, MAZE M. Prolonged hyporesponsiveness of vascular smooth muscle contraction after halothane anesthesia in rabbits. Anesth Analg 1985;64:1–6.

Halothane diminishes smooth muscle contractility in vascular tissue. In order to further characterize this phenomenon we undertook a series of in vivo and ex vivo experiments. Pressor dose–response curves to the selective α_1-adrenergic agonist, phenylephrine, were constructed in groups of rabbits before, during and 2 hr after halothane anesthesia and the dose of phenylephrine that induced a 25 torr increase in mean arterial pressure (ED_{25}) was derived by polynomial regression analysis. ED_{25} torr increased significantly during halothane anesthesia, and rabbits remained in this insensitive state when the ED_{25} was assessed 2 hr after anesthesia.

The halothane-induced loss of responsiveness was corroborated by ex vivo experiments utilizing aortic rings from halothane-anesthetized rabbits. The maximal contraction to norepinephrine (NE) was significantly lower in halothane-treated aortic rings and only slowly returned to normal by 4 hr. The EC_{50} (the dose causing a 50% maximal contraction) for NE was significantly greater in aortic rings from halothane-anesthetized rabbits. This loss of sensitivity, reflected by the higher EC_{50} was not restored by 4 hr of ex vivo incubation in a halothane-free medium. We conclude that halothane induces loss of sensitivity to adrenergic agonists that persists for several hours after termination of the halothane anesthetic.

Key Words: ANESTHETICS, VOLATILE—halothane. SYMPATHETIC NERVOUS SYSTEM—α-adrenergic responsiveness. ARTERIES, REACTIVITY.

Halothane remains a commonly used general anesthetic because of its safety (1) and ease of administration. It is widely used to facilitate instrumentation of laboratory animals prior to physiological testing in the awake state. Halothane's depressant effect on the cardiovascular system is a drawback however, because it causes a dose-dependent decrease in arterial blood pressure. This hypotension is due to halothane's negative inotropic and chronotropic actions (2–6). Additionally, the peripheral vasculature is affected by halothane (7), although the extent and direction of change varies in different vascular beds (5); splanchnic vascular resistance is enhanced while the resistance in the iliac and renal beds decreases (5). Overall, a significant decrease in the systemic vascular resistance is noted after prolonged halothane anesthesia in concentrations of 1–2.5% (4).

The mechanism whereby halothane diminishes the peripheral vascular resistance is poorly understood. Smooth muscle contractility of the vasculature is influenced by the autonomic nervous system; halothane depresses preganglionic sympathetic nerve activity (8), sympathetic ganglionic transmission (9), and postganglionic nerve transmission (9) in a dose-dependent manner. Halothane also inhibits the release of endogenous norepinephrine provoked by electrical nerve stimulation (10). All these effects result in a diminution in the available norepinephrine necessary to activate the smooth muscle and initiate the contractile process.

In addition to these indirect effects on neural vasomotor activity, halothane directly decreases the contractility of aortic strips (11–14). This in vitro halothane-induced relaxation cannot be mimicked, aborted, or prevented with known pharmacologic agonists and antagonists of smooth muscle receptors (2,12–15). It is noteworthy that the physical presence

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Address correspondence to Dr. Maze, Anesthesiology Service (112A), VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

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of halothane was necessary to induce these effects, because after halothane washout, the parameters of contractility returned promptly to normal (11,14). This rapidly reversible property is often cited as justification for the use of halothane to prepare animal models in which subsequent perturbations can be performed from a stable baseline.

However the extent to which the direct vascular depressant effect of halothane persists after terminating the anesthetic has not been established. The present study was designed to investigate, both in vivo and ex vivo, the reduction in vascular responsiveness that is present after termination of the halothane anesthetic.

Methods

In Vivo Experiments

Male New Zealand white rabbits (2.5–3.0 kg) from the same source were used for all studies. Catheters were inserted into the central artery and vein of the ear to measure mean arterial pressure (MAP), withdraw blood, and inject drugs. Maintenance intravenous fluids consisted of 5% dextrose in 0.2N saline at a rate of 4 $ml \cdot kg^{-1} \cdot hr^{-1}$. At least 20 min were allowed to elapse after the cannulation before experimental manipulations began.

Blood pressure response curves to the selective α_1-adrenergic agonist, phenylephrine, were defined according to a modification of the method of Hamilton and Reid (16). Phenylephrine, 100 μg/ml, was infused (Harvard syringe pump) over 1 min, and the highest MAP achieved was noted from a recording of the blood pressure response. After 5 min, the MAP returned to the basal state. Logarithmically spaced incremental doses, ranging from 12.5 to 200 μg/min, were infused, and the transduced MAP was recorded on a direct writing oscillographic recorder (Beckman R-511A). The phenylephrine log dose pressor–response curves were derived by polynomial regression (17), and the dose of phenylephrine corresponding to a 25 mm Hg increase in MAP (ED_{25}) was calculated.

The ED_{25} was selected as our measure of α-adrenergic responsiveness for a number of reasons. In our in vivo model, phenylephrine at the highest dose (200 μg/min) induced vasoconstriction to the extent that the arterial trace dampened out, precluding a reliable measurement of blood pressure in the awake animal. Therefore, we were able to assess neither the maximal response, nor the dose of agonist necessary to induce the half-maximal response. These two parameters, which are most useful in describing changes in adrenergic responsiveness, can only be derived when data from the full dose–response curve are available. Secondly, phenylephrine, especially at higher doses, may enhance blood pressure by increasing myocardial contractility (18). Thus the phenylephrine-induced pressor effect may not solely reflect an increase in systemic vascular resistance at higher increments in blood pressure. Furthermore, counterregulatory mechanisms, such as bradycardia, are invoked after moderate elevations in blood pressure.

Group I rabbits (n = 7) were awake controls. In this group, the dose pressor–response assessment was performed at 0 min and repeated after 3 and 6 hr. In group II rabbits (n = 7), a preanesthetic dose–response to phenylephrine was performed. Anesthesia was induced in this group by mask inhalation of halothane in oxygen delivered through a modified Ayre's T-piece in high enough flow rates to insure a nonrebreathing circuit. After endotracheal cannulation (19) with a cuffed 3.0 inner diameter endotracheal tube, ventilation was controlled with a volume-limited ventilator at a rate of 35 breaths/min to maintain the end-tidal CO_2 in the normocarbic range as measured by an infrared analyzer (Beckman LB-2). This was confirmed by measurement of arterial blood-gas tensions. Anesthesia was maintained with a halothane concentration of 1.6% vol/vol (2 MAC of halothane for rabbits) (20) as determined by infrared gas analysis. Temperature (rectal) was maintained at 38.5°C with heating lamps and warming blankets where appropriate. After 2 hr of anesthesia, the phenylephrine dose–response curve was defined. Thereafter, halothane was discontinued, the rabbit was extubated and recovered, and 2 hr later, the phenylephrine dose–response curve was repeated.

An additional unanesthetized awake group of rabbits (group III, n = 8) was employed to mimic the hypotension that occurs during and after halothane anesthesia. Arterial hypotension was induced in conscious rabbits with a combination of trimethaphan (25–50 μg/min) and sodium nitroprusside (1.3–3 μg/min) to achieve approximately the same MAP, over the same time period, that was obtained during halothane anesthesia (32 torr). The dose–response curve to phenylephrine was determined. The vasodilators were then adjusted to maintain the MAP at the level noted after termination of halothane anesthesia (52 torr) in the group II rabbits. After 2 hr the phenylephrine dose–response curve was repeated. Plasma catecholamine concentrations were measured by high performance liquid chromatography (21) in the rabbits in the awake, anesthetized, postanesthetized, and hypotensive states immediately before the phenylephrine dose pressor–response assessments were undertaken.

Ex Vivo Experiments

Ten unanesthetized rabbits were given 1000 units of heparin subcutaneously and were sacrificed 15–20 min later by concussion and cardiac excision. Thoracic aortas were rapidly dissected free, cleaned of all adherent connective tissues and placed in modified Kreb's solution of the following composition (in mM): NaCl 118.2; KCl 4.6; $CaCl_2$ 2.5; $MgSO_4$ 1.2; $NaHCO_3$ 24.8; KH_2PO_4 1.2; glucose 10.0; and bubbled with a gas mixture containing 95% O_2 and 5% CO_2, pH 7.4 (22). The buffer was changed 20 times during the experiment. Aortic rings (3-mm wide) were mounted in a 25-ml jacketed tissue bath kept at 37.5–38°C. An initial resting tension of 1.0 g was applied and the rings were allowed to equilibrate for 2 hr before exposure to drug. Responses were recorded as changes in grams of tension on a physiological recorder with a strain-gauge force displacement transducer (UC-3, Gould). Cumulative dose–response curve for norepinephrine and histamine were performed by producing a stepwise increase in concentration of each drug as soon as a steady response was obtained from each preceding dose.

The EC_{50} and maximal contractions (E_{max}) were determined by a best fit of the four-parameter logistic equation (23) on a Hewlett Packard 9816 computer. Another 5 animals were anesthetized with halothane as described in the in vivo experiments. After 2 hr of anesthesia, the thoracic aorta was removed, and the contractility in the aortic rings measured as above at 2 and 4 hr after removal. For both the in vivo and ex vivo experiments, data were compared by the two-tailed paired and unpaired t-test where appropriate. $P < 0.05$ was considered statistically significant.

Results

In Vivo Experiments

Results for the in vivo experiments are tabulated in Table 1. The ED_{25} in group I animals (normotensive, awake) did not change significantly at 0, 3, or 6 hr (Table 1). These data indicate that our model of α-adrenergic responsiveness is reproducible and stable over this time and showed no change with repeated testing. In the halothane-treated rabbits the ED_{25} during anesthesia (107 ± 20 μg/min) was significantly ($P < 0.01$) higher than that observed in the preanesthetic state (70 ± 22 μg/min). This insensitivity to phenylephrine, as reflected by the higher ED_{25}, persisted for a further 2 hr after the termination of the halothane anesthetic (134 ± 29 μg/min) (Table 1, Fig. 1). In group III rabbits, hypotension was induced to the same degree as that seen during (MAP 32 torr) and after (MAP 53 torr) halothane anesthesia. When compared with these hypotensive awake rabbits, the halothane-treated rabbits had a significantly ($P < 0.001$) higher ED_{25} (Table 1, Fig. 1). Plasma catecholamine concentrations (Table 2) did not differ significantly at the times measured under the various experimental conditions of awake, anesthetized, postanesthetic, and hypotensive states.

Table 1. Phenylephrine Dose–Pressor Response (ED_{25})[a]

Group	n[b]	μg/min	P
I[c]—control			
0 hr	7	83 ± 35	
3 hr	7	87 ± 26	NS
6 hr	7	79 ± 30	NS
II[d]—halothane			
Pre	7	70 ± 22	
During	7	107 ± 20	<0.01[f]
After	7	134 ± 29	>0.05[g]
III[e]—hypotension			
MAP 32 torr	8	40 ± 7	<0.001[h]
MAP 53 torr	8	28 ± 5	<0.001[i]

[a] Dose of phenylephrine (mean ± SD) causing a 25 torr increase in MAP. [b] Number of animals. [c] Normotensive awake animals tested at 0, 3, and 6 hr. [d] Animals tested before, during, and 2 hr after halothane anesthesia. [e] Hypotensive awake animals tested at similar blood pressures to during (32 torr) and after (53 torr) halothane anesthesia. [f] Paired comparison of during vs control. [g] Paired comparison of during vs after anesthesia. [h] Unpaired comparison with during anesthesia in group II. [i] Unpaired comparison with after anesthetic in group II.

Ex Vivo Experiments

Responses of aortic rings to norepinephrine are presented in Table 3 and Figure 2. Two hours after halothane anesthesia, the sensitivity (EC_{50}) and the E_{max} are markedly reduced compared to controls. After 4 hr of ex vivo incubation, the E_{max} was not different from controls, but EC_{50} was still significantly increased compared to controls. The histamine response curves (Table 3 and Fig. 2 (lower panel)) showed no change in sensitivity after halothane anesthesia, but the E_{max} was reduced at 2 hr and returned to control values after 4 hr of ex vivo incubation.

Discussion

Using a combination of in vivo and ex vivo techniques, our data demonstrate adrenergic hyporesponsiveness in vascular tissue during halothane anesthesia that is only slowly reversible after termination of the anesthetic. Responsiveness of α-adrenoceptors can be assessed by using incremental infusions of specific agonists such as phenylephrine (16). We chose this noninvasive assessment of the in vivo responsiveness of the circulation because of its sim-

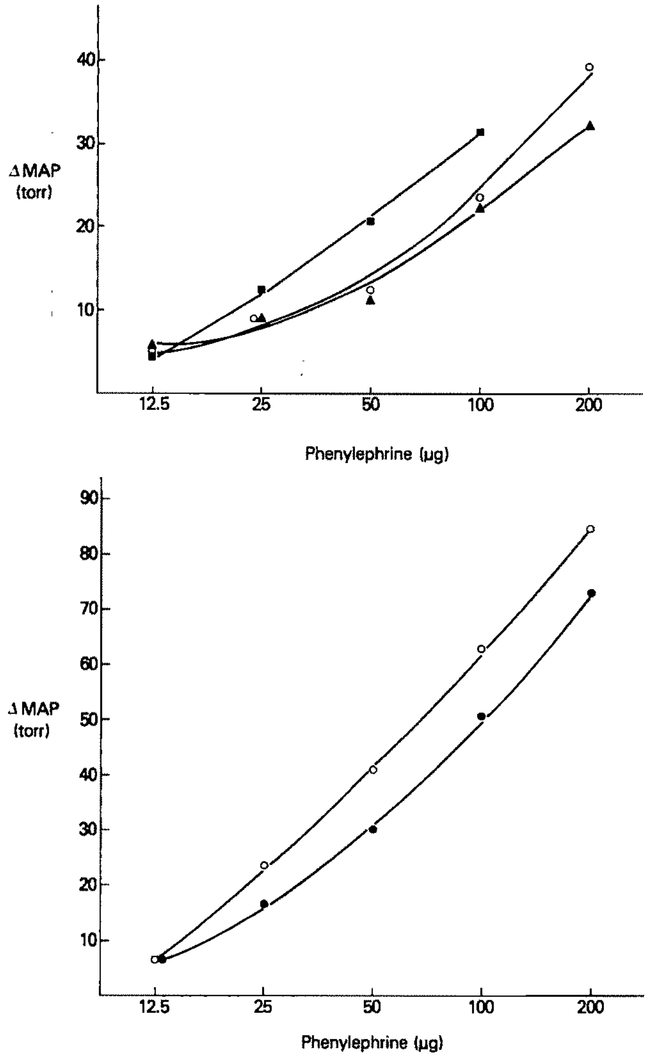

Figure 1. *Upper panel*: phenylephrine dose pressor–response curves in rabbits before anesthesia (■——■), during halothane anesthesia (○——○), and 2 hr after the termination of the halothane anesthetic (▲——▲). *Lower panel*: phenylephrine dose pressor–response curves in unanesthetized rabbits in which the starting MAP was adjusted to the same level as noted during halothane anesthesia, 32 torr, (●——●) and 2 hr after terminating halothane anesthesia, 53 torr, (○——○).

Table 2. Plasma Catecholamines in Anesthetized and Awake Rabbits

	n^a	Epinephrine[b]	Norepinephrine[b]
Halothane[c]		pg/ml	pg/ml
Pre	7	60 ± 57	306 ± 119
During	7	34 ± 28	271 ± 111
After	7	42 ± 31	269 ± 143
Awake[d] III			
Normotensive	8	55 ± 57	205 ± 121
MAP 32 torr	8	34 ± 23	164 ± 114
MAP 52 torr	8	35 ± 24	175 ± 131
P^e		NS	NS

[a] Number of animals. [b] Mean ± SD. [c] Catecholamines measured before, during, and 2 hr after halothane anesthesia. [d] Catecholamines measured before (normotensive) and during induced hypotension with trimethaphan and sodium nitroprusside. These hypotensive animals were tested at blood pressure levels similar to those observed during (32 torr) and after (53 torr) halothane anesthesia. [e] There were no statistically significant inter- or intragroup differences.

plicity and because we could confirm these effects directly in the accompanying ex vivo experiments.

Because baroreflexes to phenylephrine-induced pressor effects may vary at different absolute MAP values, we employed an induced hypotensive awake group of rabbits as an additional control for the group II (anesthetized) animals. Although the mechanisms of hypotension during halothane anesthesia and from a combination of trimethaphan and sodium nitroprusside differ, the sympathoadrenal response, as reflected by plasma catecholamine levels, was similar in all hypotensive animals. Thus the diminished response observed in the halothane anesthetized animals cannot be explained by increased levels of circulating neurotransmitter inducing desensitization. Given that the effects of halothane on baroreceptor responsiveness are severely depressed (24,25), the much smaller pressor response to phenylephrine in the halothane-treated rabbits is even more prominent.

The most startling finding of our study is the prolonged period of α-adrenergic hyporesponsiveness after halothane anesthesia. In the in vivo state, at 2 hr after termination of halothane anesthesia, the dose of phenylephrine necessary to increase the MAP by 25 torr was still significantly greater than the preanesthetic or hypotensive controls. After 2 hr of anesthesia at 2.0 × MAC of halothane for the rabbit, considerable amounts of this lipophilic agent have partitioned into fat stores. Recent fluorine-19 nuclear magnetic resonance studies show that halothane is detectable in the brain up to 96 hr after a short anesthetic (26). Even though rabbits have rapidly regained consciousness, the cardiovascular depressant effects unexpectedly remain.

In an earlier in vitro study, Clark and MacCannell showed that halothane decreased the maximal response of rabbit aortic strips to norepinephrine (14). The responsiveness to adrenergic agonists could be promptly restored to normal after a 30 min washout with a halothane-free medium. However, the reversibility of the ex vivo hyporesponsiveness is much slower when the aorta is exposed to halothane in vivo. We speculate that hepatic biotransformation of halothane produces metabolites that may be more difficult to expunge from the tissue ex vivo than the parent compound. Experimental evidence to support this contention includes the week-long elevation in bromide excretion after halothane anesthesia (27).

Table 3. Responsiveness of Aortic Rings to Norepinephrine and Histamine[a]

	n[b]	Norepinephrine		Histamine	
		EC_{50}[c] (μM)	E_{max}[d] (g)	EC_{50}[c] (μM)	E_{max}[d] (g)
Control[e]	10	0.03 ± 0.01	6.93 ± 0.15	2.66 ± 0.27	7.12 ± 0.23
Halothane[f]					
2 hr	5	0.11 ± 0.02[g]	5.05 ± 0.86[h]	2.41 ± 0.10	5.29 ± 0.08[i]
4 hr	5	0.09 ± 0.02[g]	7.21 ± 0.72	2.58 ± 0.17	7.21 ± 0.42

[a] Ex vivo contractile response of aortic rings to norepinephrine and histamine in water bath (mean ± SD). [b] Number of experiments. Each experiment was performed in duplicate. [c] EC_{50} is the dose of agonist eliciting the half maximal response. [d] E_{max} is the maximal contraction achieved. [e] Rabbits were sacrificed and thoracic aortas harvested for contractile responses after 2 hr of ex vivo incubation. [f] Halothane-anesthetized rabbits were sacrificed, thoracic aortas harvested, and contractile responses measured after 2 and 4 hr of ex vivo incubation. [g] $P < 0.001$. [h] $P < 0.002$. [i] $P < 0.005$.

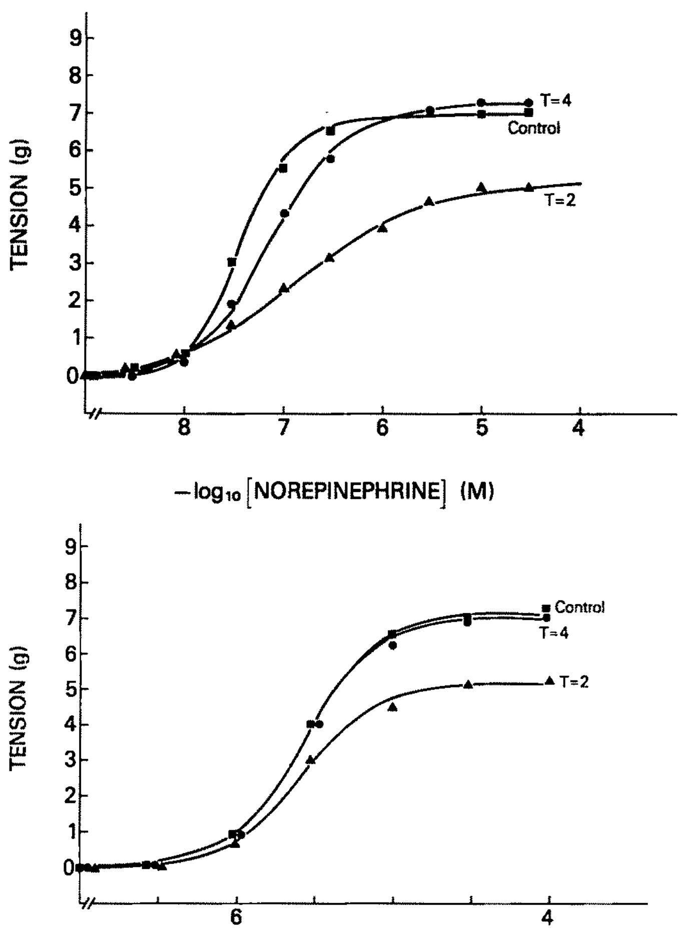

Figure 2. Ex vivo dose–response curves to norepinephrine (*upper panel*) and histamine (*lower panel*) in aortic rings. Changes, in grams of tension displaced, in response to norepinephrine or histamine were recorded in tissue from unanesthetized rabbits (control) and in halothane-treated rabbits after 2 hr (t = 2) and 4 hr (t = 4) of ex vivo incubation.

The persistent vascular hyporesponsiveness that we demonstrated may be dose- and exposure-time dependent. Thus a lesser effect may be demonstrable at lower halothane concentrations delivered for a shorter duration.

Halothane induces a heterologous loss of sensitivity (28) in the aortic rings because the maximal response to histamine as well as norepinephrine is reduced. Thus the site at which halothane decreases contractility probably lies distal to the smooth muscle receptor. Halothane has widespread effects on calcium ion translocation resulting in a disruption of the coupling of excitation and contraction (13) that may constitute the basis for its cardiovascular depressant action.

The implications of our data are twofold. Halothane should probably not be used to facilitate instrumentation of animals in which subsequent cardiovascular physiological experiments are to be conducted. If it is necessary to use halothane for this purpose, then the onus is on the investigator to demonstrate that residual hyporesponsiveness no longer pertains. While we noted a persistent effect for at least 2 hr, this may last longer as indicated by the ex vivo experiment. Secondly, because of the apparent loss of responsiveness, higher doses of vasopressor agents may be needed to treat hypotension during and after halothane anesthesia.

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1985;64:7–10

Effects of Verapamil on Uterine Blood Flow and Maternal Cardiovascular Function in the Awake Pregnant Ewe

Suha H. N. Murad, MD, Khalil M. A. Tabsh, MD, Genady Shilyanski, MD,
Patricia A. Kapur, MD, Chiache Ma, MD, Chingmuh Lee, MD, and
Kenneth A. Conklin, MD, PhD

MURAD SHN, TABSH KMA, SHILYANSKI G, KAPUR PA, MA C, LEE C, CONKLIN KA. Effects of verapamil on uterine blood flow and maternal cardiovascular function in the awake pregnant ewe. Anesth Analg 1985;64:7–10.

Calcium entry blocking drugs may have a role in the treatment of maternal and fetal tachyarrhythmias, as well as for treatment of premature labor. This study was undertaken to assess the hemodynamic effects of verapamil in the awake pregnant ewe. Verapamil, 0.2 mg/kg administered intravenously over 3 min, resulted in the following maternal cardiovascular changes: transient (2 min) but significant decreases in systolic, diastolic, and mean blood pressures, and significant but equally transient increases in central venous pressure and mean pulmonary arterial pressure. Pulmonary capillary wedge pressure increased for 5 min. These results are consistent with the negative inotropic and peripheral vasodilating effects of verapamil. Cardiac output, systemic vascular resistance, and pulmonary vascular resistance were unaffected. Uterine blood flow decreased 25% at 2 min and remained significantly (7–18%) below control levels for 30 min after drug injection. The effects of verapamil on uterine blood flow suggest that it should be used with caution in cases where uteroplacental perfusion is compromised.

Key Words: ANESTHESIA—obstetric. HEART, pharmacology—verapamil.

Calcium channel blocking drugs have been recently introduced for treatment of supraventricular tachyarrhythmias and Prinzmetal's angina (1). They also have a role in the management of angina pectoris and systemic hypertension, and for control of the ventricular rate in atrial fibrillation and flutter (1,2). Although not as yet approved for such uses, these agents may also prove effective as a means of producing induced hypotensive anesthesia, for treatment of both cerebral artery vasospasm and pulmonary artery hypertension, for myocardial protection during global ischemia (1), and for management of postresuscitation brain injury (3). Calcium channel blockers act by inhibiting the inward flux of calcium through the slow ionic channel of excitable cell membranes during the action potential (1). This action interferes with the excitation–contraction coupling in vascular smooth muscle producing coronary and peripheral vasodilation. In cardiac muscle, this action results in a negative inotropic effect. These agents also produce prolongation of conduction time in the sinoatrial and atrioventricular nodes.

In obstetrics, one of the calcium channel blockers (verapamil) has been used to treat supraventricular tachycardia in the fetus to prevent heart failure and hydrops fetalis (4). Calcium blockers have also been used as tocolytic agents (5). Because these agents produce peripheral vasodilation and reduce mean arterial pressure (6–12), one might anticipate a decrease in uterine perfusion pressure and a reduction in uterine blood flow. This effect could be detrimental to the fetus, especially if uteroplacental perfusion is already compromised. The objective of our investigation was to evaluate the effects of verapamil on maternal hemodynamics in the chronically instrumented awake pregnant ewe. Of specific interest was a determination of the effects of this drug on uterine blood flow.

Methods

Eight ewes with singleton pregnancies of 120–130 days gestation (cared for according to the research council's

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Address correspondence to Dr. Murad, Department of Anesthesiology, Harbor/UCLA Medical Center, 1000 Carson Street, Torrance, CA 90509.

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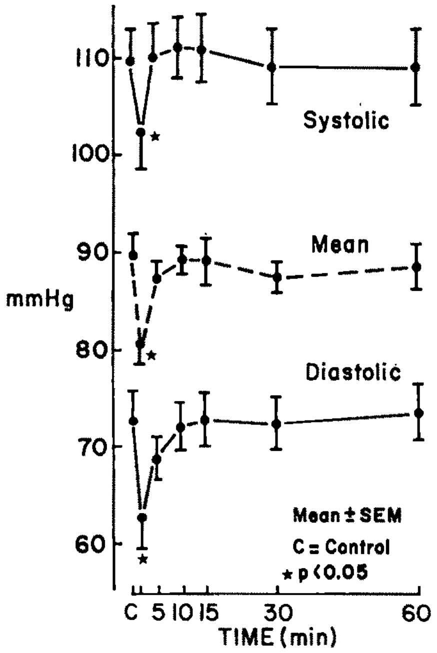

Figure 1. Maternal systolic, mean, and diastolic blood pressures before (C) and at various times after intravenous injection of verapamil.

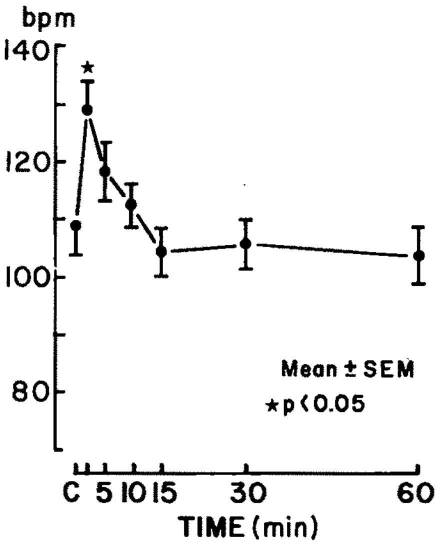

Figure 2. Maternal heart rate before (C) and at various times after intravenous injection of verapamil.

guide for the care and use of laboratory animals) were instrumented under local anesthesia and diazepam sedation as follows: a femoral arterial catheter for blood pressure monitoring; a femoral venous catheter for intravenous fluid and drug administration; and an internal jugular venous cannula for insertion of a pulmonary arterial thermodilution catheter (Model 93A-131-7F) on the day of the experiment. An electromagnetic flow probe (Dienco) was placed around the middle uterine artery, and flow was recorded with a Dienco RF 2100 flowmeter. Animals were allowed to recover for 5 days.

On the day of the experiment, the ewe was allowed to stand quietly in her cage for one hour while Ringer's lactate solution was infused at the rate of 3 ml/min. The following were then measured and recorded on an 8-channel Beckman recorder: heart rate (HR), blood pressure, pulmonary arterial pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and uterine arterial blood flow (UBF). Systemic (SVR) and pulmonary vascular resistances (PVR) were calculated. Cardiac output (CO) was measured by thermodilution using an American Edwards cardiac output computer (Model 9510). After baseline measurements were recorded, the animal received verapamil (Isoptin), 0.2 mg/kg, infused over a period of 3 min. Hemodynamic responses were then recorded for 1 hr. A total of 12 experiments were done. If an animal was used more than once, there was a 3-day interval between one experiment and the next. No animal was used for more than two experiments. Statistical analysis was performed by analysis of variance for repeated measures and Bonferoni *t*-test, with a value of $P < 0.05$ being considered as statistically significant.

Results

Intravenous injection of verapamil caused a significant (14%) decrease in maternal diastolic blood pressure (DBP) at 2 min (Fig. 1). At 5 min DBP was not significantly different from control. Systolic blood pressure (SBP) was 7% below control at 2 min and returned to control levels thereafter. This decrease, although small, was statistically significant. Mean arterial blood pressure (MAP) decreased significantly (11%) at 2 min but was not significantly different from control after that time. Maternal HR increased significantly from 109 to 129 beats/min 2 min after drug injection. Thereafter it was not significantly different from control (Fig. 2).

Mean pulmonary artery pressure (MPAP) was elevated significantly at 2 min after verapamil injection. PCWP was elevated significantly for the first 5 min. Thereafter both MPAP and PCWP returned to control levels (Fig. 3). CVP increased significantly from 3.4 to 6.4 mm Hg (88%) at 2 min, but was not significantly different from control thereafter (Fig. 3). There were no significant changes in CO (Fig. 5), SVR (Fig. 5), or PVR (Fig. 5) throughout the experimental period.

Uterine arterial blood flow (UBF) decreased 25% below control levels at 2 min and was 18% below

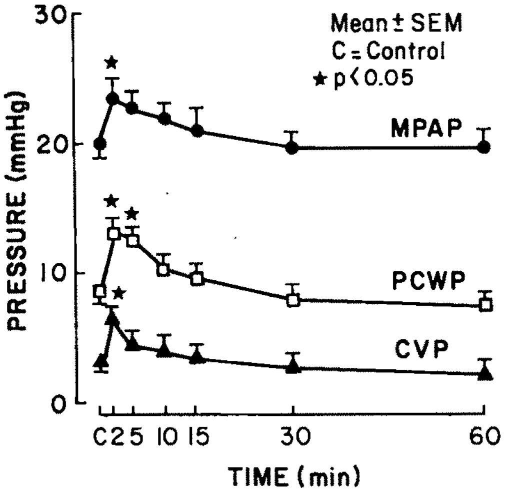

Figure 3. Mean pulmonary arterial (●), pulmonary capillary wedge (□), and central venous (▲) pressures before (C) and at various times after intravenous injection of verapamil.

control at 5 min (Fig. 4). It remained approximately 10% below control for the remainder of the experimental period. The decreases in UBF were significantly below control levels for 30 min after the administration of verapamil.

Discussion

Verapamil, in a dose comparable to that used to treat supraventricular tachyarrhythmias in humans (0.2 mg/kg), produced hemodynamic changes in the awake pregnant ewe that are consistent with its effect on the myocardium and vascular smooth muscle. Intravenous injection of verapamil resulted in direct myocardial depression as evidenced by elevation of CVP, MPAP, and PCWP. This effect, however was short-lived, lasting 5 min or less. These results are consistent with observations of others that demonstrate the negative inotropic effects of this drug (6–9), i.e., decreased dP/dt_{max}. Cardiac output, however, did not decrease significantly from control at any time during the experiment. Others have also shown that CO is unchanged, or even elevated when verapamil is administered intravenously to conscious (7,8) or anesthetized (10,11) dogs, anesthetized swine (9), and awake humans (12). The maintenance or elevation of CO is attributed to the increased HR that results from elevated plasma levels of catecholamines (13), and most likely accounts for the lack of significant change in CO in our experiments. The sympathetic nervous system response to verapamil that causes this effect results from decreased peripheral resistance and is mediated via the baroreceptor reflexes.

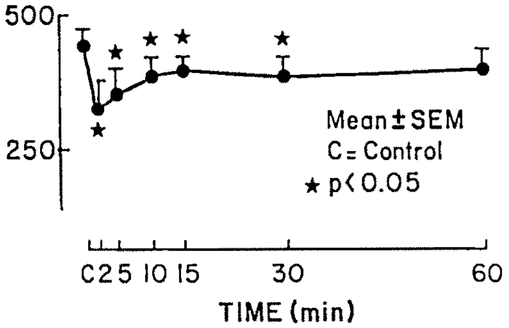

Figure 4. Uterine arterial blood flow (ml/min) before (C) and at various times after intravenous injection of verapamil.

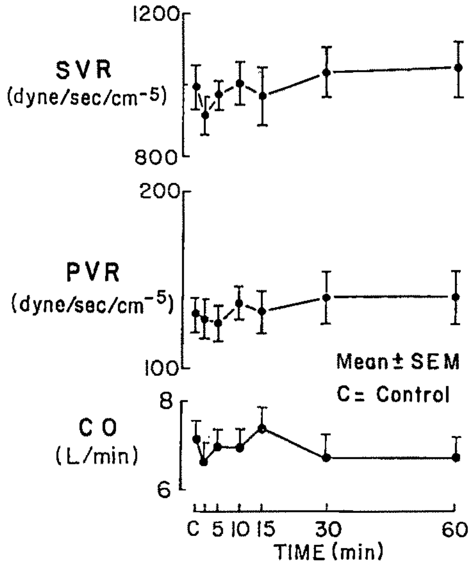

Figure 5. Systemic vascular resistance (SVR), cardiac output (CO), and pulmonary vascular resistance (PVR) before (C) and after intravenous injection of verapamil.

Intravenous injection of verapamil in the awake pregnant ewe produced transient peripheral vasodilation as evidenced by the decreases in SBP, DBP, and MAP (for 2 min). These results are comparable in both magnitude and duration to those observed by others in conscious dogs (6–8), awake humans (12), swine anesthetized with nitrous oxide (9), dogs anesthetized with nitrous oxide and pentobarbital (10), and dogs anesthetized with pentobarbitol alone (11). The transient nature of the hypotensive response can be attributed to rapid decreases in plasma levels of verapamil after its intravenous injection. In swine anesthetized with halothane, however, MAP is decreased significantly for a longer period of time (9). This effect is likely due to the additive hemodynamic effects of halothane and verapamil, and may include halothane suppression of the baroreceptor reflex (9).

Use of calcium blockers in the pregnant patient for treatment of fetal tachyarrhythmias (4) and for tocolysis (5) raises questions as to the safety of these agents with respect to fetal well-being. Some studies suggest that drugs that produce peripheral vasodilation (such as verapamil) might reduce UBF by decreasing MAP and uterine perfusion pressure (UPP), an effect that is not unexpected because UBF is not maintained by autoregulation (14). Nitroglycerin (NTG), for example, substantially reduces UBF in the anesthetized pregnant ewe (15), while both NTG and sodium nitroprusside (16) produce small (but not statistically significant) reductions in UBF in the awake pregnant ewe model. In our experiments, UBF decreased 25% at 2 min, 18% at 5 min, and remained significantly (10%) below control levels for the next 25 min. This decrease in UBF most likely resulted from decreases in MAP and UPP, although uterine vasoconstriction by catecholamines released by verapamil (13) may have also contributed to this effect. Although the degree of reduction in UBF observed should not compromise the normal fetus, it may not be tolerated by a fetus that is already compromised by impaired uteroplacental perfusion or placental insufficiency. Care, however, should be taken in extrapolating these results to what might be observed in humans.

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Assessment of Age-related Acid Aspiration Risk Factors in Pediatric, Adult, and Geriatric Patients

Laxmaiah Manchikanti, MD, Jerry A. Colliver, PhD, Teresa C. Marrero, CRNA, and James R. Roush, MD

MANCHIKANTI L, COLLIVER JA, MARRERO TC, ROUSH JR. Assessment of age-related acid aspiration risk factors in pediatric, adult, and geriatric patients. Anesth Analg 1985;64:11–7.

One hundred inpatients scheduled for elective surgery were studied to determine the age-related risk of pulmonary aspiration as indicated by gastric acidity and volume. Twenty-five patients from 6 months to 12 years old were included in the pediatric age group, 50 patients from 18 to 64 years old were included in the adult age group, and 25 patients older than 65 years old were included in the geriatric group. Mean gastric pH was 1.99, 2.40, and 3.32 in the pediatric, adult, and geriatric age groups, respectively; the differences between the three groups were statistically significant. The proportions of patients with pH $\leqq$ 2.50 were also significantly different among three groups: 92%, 76%, and 60% in the pediatric, adult, and geriatric age groups, respectively. Mean gastric volumes were 0.49, 0.37, and 0.24 ml/kg and proportions of patients with volumes $\geqq$ 0.40 ml/kg were 60, 32, and 12% in pediatric, adult, and geriatric patients, respectively. Gastric contents with both pH $\leqq$ 2.5 and volume $\geqq$ 0.4 ml/kg were seen in 60, 28, and 12% in the three respective groups. Risk of acid aspiration pneumonitis theoretically is present in all age groups, with children being at greatest risk and geriatric patients with least risk. We have also noted a correlation between age and gastric contents because gastric acidity and volume both decreased as age increased. Increasing length of fasting period increased gastric acidity without significant effect on volume.

Key Words: GASTROINTESTINAL TRACT—stomach, pH and volume. AGE—gastric pH and volume.

Vomiting or regurgitation of stomach contents with subsequent aspiration is a major cause of anesthesia-related morbidity and mortality. Danger of acid pneumonitis has been well recognized as a particular hazard in both surgical and obstetric patients requiring emergency surgery (1–4). However, numerous investigators during the last decade also have demonstrated that 60–100% of children, outpatients, obese patients, and nonobese inpatients undergoing elective surgery, have highly acidic gastric contents before induction of anesthesia despite overnight fasting (4–9).

A gastric pH below 2.5 and gastric volume of 0.4 ml/kg are considered as critical factors for the development of pulmonary injury (2,3). Studies of children and separately conducted studies of adults have shown differences in frequency of low gastric pH and high gastric volume with potentially greater risk of acid aspiration pneumonitis in pediatric patients (5,8). In addition, various factors combine to make infants and children more susceptible to regurgitation and aspiration than adults (10). Risk of acid pneumonitis may be increased in geriatric patients, secondary to increased frequency of hiatal hernias (11), increased incidence of gastroesophageal reflux (12), and a decrease in gastric motility (13). We are not aware of any clinical studies evaluating acid aspiration risk factors in relation to age. Hence, we have undertaken this prospective evaluation to investigate and compare the incidence of acid aspiration risk in three groups of patients, namely pediatric, adult, and geriatric patients.

Methods

This study was carried out with 100 inpatients scheduled for elective surgery under general anesthesia. The protocol was approved by the Institutional Review Committee. Informed consent was obtained from patients or parents. Only patients without gastrointestinal disorders and nonobese patients were included in the study. Obesity was defined as body

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Address correspondence to Dr. Manchikanti. Department of Anesthesiology, Lourdes Hospital, 1530 Lone Oak Road, Paducah, KY 42001.

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Table 1. Patient Characteristics

		Pediatric age group ($\leqq$ 12 yr)	Adult age group ($\geqq$ 18–< 65 yr)	Geriatric age group (> 65 yr)	Directions and significance of difference
Number		25	50	25	
Age (yr)	Mean ± SEM	6.2 ± 0.7	38.8 ± 2.0	73.9 ± 1.2	P < A < G
	Range	0.81–12	18–64	68–88	
Height (cm)	Mean ± SEM	—	171.7 ± 1.4	169.8 ± 1.9	A = G
	Range	—	154.9–193.0	152.4–188.0	
Weight (kg)	Mean ± SEM	24.6 ± 2.8	68.5 ± 2.3	68.3 ± 2.5	P < A = G
	Range	6.8–58.1	45.5–110.0	40.8–86.0	
Fasting period (min)	Mean ± SEM	588 ± 20	639 ± 19	644 ± 30	P = A = G
	Range	480–780	480–960	480–930	

Abbreviations: P, pediatric; A, adult; G, geriatric; > and <, significant difference; =, no significant difference.

weight 20% above the ideal weight (14). All patients fasted for a minimum of 8 hr before induction of anesthesia and received either intramuscular premedication with meperidine and hydroxyzine, or meperidine and droperidol, or no premedication. None of the patients received anticholinergics, antacids, H_2-receptor antagonists, or gastrokinetic agents. Twenty-five patients from 6 months to 12 years old were included in the pediatric group, 50 patients from 18 to 64 years old were included in the adult age group, and 25 patients older then 65 years old comprised the geriatric group.

After induction of anesthesia and stabilization of the condition of the patient, an appropriate size (#14 or #18) Salem Sump tube was passed into the stomach and gastric contents were evacuated into a mucus trap by suction. The position of the gastric tube was verified by auscultation of epigastrium with insufflation of air through the tube. The amount of gastric juice was measured by graduations on the mucus trap and the pH was determined by a Corning pH meter with an Ag/AgCl probe combination electrode.

Patients with gastric pH $\leqq 2.5$ and/or volume $\geqq 0.4$ ml/kg were defined as at risk of pulmonary damage in the event of aspiration. Incidences of gastric pH $\leqq 1.8$ and > 5.0 and gastric volumes 0.1 ml/kg, 0.2 ml/kg, 0.3 ml/kg, and 0.75 ml/kg were also studied. Risk factors were analyzed independently and in combination. In addition, each patient's pH reading was transformed to an H^+ concentration and analyses were performed on the H^+ values.

Statistical analyses were performed by analyses of variance (ANOVA) and χ^2-square tests. One way ANOVAs with Duncan's multiple range follow-up tests were used to compare statistically the three age groups in terms of mean pH and mean volume. The proportions of patients defined as being "at risk" in the three groups were compared with χ^2-tests of independence. Polynomial regressions were used to determine the nature and extent of the relationships of gastric pH and volume with age and length of fasting period. Results were considered statistically significant when P values were less than 0.05.

Results

Demographic data of the three age groups are presented in Table 1. Patients in all three age groups were comparable with respect to sex distribution and length of fasting period. The three groups differed significantly in terms of mean age. Mean weight was significantly less in pediatric patients, but was not significantly different in the adult and geriatric patients.

Gastric pH

The mean pH in the geriatric group was significantly greater than those in the pediatric and adult groups ($P < 0.05$) (Table 2). However, mean pH levels in the pediatric and adult groups did not differ significantly. A polynomial regression of gastric pH on age performed on the pooled data for the three groups revealed a significant linear trend, $P = 0.0115$, showing that as age increased, pH increased (Fig. 1).

The groups also differed significantly in terms of the proportion of patients with pH $\leqq 2.50$ ($P = 0.0299$). Specifically, the proportion of pediatric patients with pH $\leqq 2.50$ was significantly greater than that of geriatric patients ($P < 0.05$). However, the proportion of adults with pH $\leqq 2.50$ did not differ significantly from the proportions in the pediatric and geriatric groups. Similar significant and nonsignificant results were obtained for the proportion of patients with gastric pH > 5.0. The proportions of patients with pH $\leqq 1.80$ did not differ significantly among the three groups.

Analysis of hydrogen ion concentration revealed significant differences among the three groups ($P = 0.0367$). Mean H^+ in the adult group was significantly

Table 2. Gastric pH Levels

		Pediatric age group	Adult age group	Geriatric age group	Directions and significance of differences
pH	Mean ± SEM	1.99 ± 0.07	2.40 ± 0.22	3.32 ± 0.42	P = A < G
	Range	1.43–3.05	1.25–7.27	1.49–7.44	
H^+ Concentration	Mean ± SEM	1.30 ± 0.17	1.81 ± 0.21	1.04 ± 0.22	P = A; P = G;
$H^+ \times 10^2$ [a]	Mean pH of H^+	1.89	1.74	1.98	A > G
Patients with pH ≦ 1.8		7 (28%)	25 (50%)	9 (36%)	P = A = G
Patients with pH ≦ 2.5		23 (92%)	38 (76%)	15 (60%)	P = A; A = G; P > G
Patients with pH > 5.0		0 (0%)	5 (10%)	6 (24%)	P = A; A = G; P > G

[a] H^+ Concentration g mEq/L. Abbreviations as in Table 1.

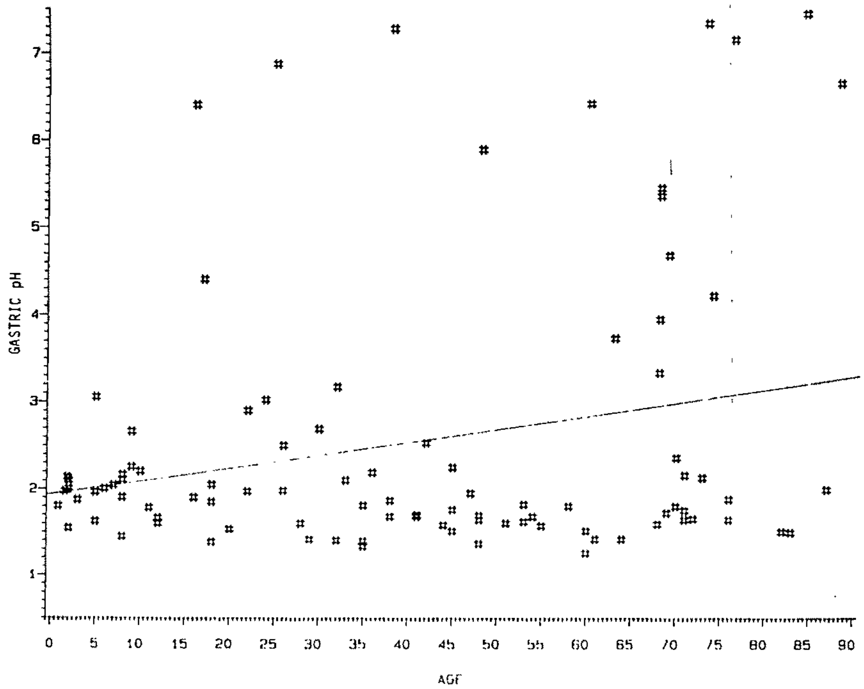

Figure 1. Relationship of gastric pH to age. A polynomial regression of gastric pH on age, showing increasing pH with increasing age.

greater than that in the geriatric group ($P < 0.05$). But the pediatric group did not differ significantly from the other two groups. These mean H^+ concentration results are not consistent with the mean pH results. This discrepancy is explained because such anomalies can occur with nonlinear transformations like negative logarithm.

Gastric Volume

The ratio between gastric volume and body weight in ml/kg was determined for each patient (Table 3). The three groups differed significantly with respect to mean gastric volume to body weight ratio ($P = 0.0046$). Although mean volume decreased from pediatric through adult to geriatric patients, the decrease was statistically significant only between pediatric and geriatric patients ($P < 0.05$). Adult patients did not differ significantly from either pediatric or geriatric group patients. A polynomial regression performed on the pooled data for the three groups combined revealed significant linear trend, $P = 0.0001$, showing that as age increased, the ratio between gastric volume and body weight decreased (Fig. 2).

The three groups differed significantly in terms of the proportions of patients with gastric volumes ≧ 0.4 ml/kg ($P = 0.0001$). The proportion of patients with volumes ≧ 0.4 ml/kg decreased significantly from the pediatric group to adults and from adults to the geriatric group ($P < 0.05$). This proportion of patients with volume ≧ 0.4 ml/kg in the geriatric group was significantly less than in the pediatric group ($P < 0.05$). Similar results were obtained for the proportion of patients with gastric volumes ≧ 0.2 ml/kg and 0.3

Table 3. Gastric Volumes

	Pediatric age group	Adult age group	Geriatric age group	Directions and significance of difference
Mean ± SEM (ml/kg)	0.49 ± 0.04	0.37 ± 0.04	0.24 ± 0.05	P = A; A = G; P > G
Range	0.21–1.15	0.05–1.33	0.04–1.12	
Patients with volume ≧ 0.1 ml/kg	25 (100%)	45 (90%)	20 (80%)	P = A; A = G; P > G
Patients with volume ≧ 0.2 ml/kg	25 (100%)	33 (66%)	11 (44%)	P > A > G
Patients with volume ≧ 0.3 ml/kg	21 (84%)	24 (48%)	5 (20%)	P > A > G
Patients with volume ≧ 0.4 ml/kg	15 (60%)	16 (32%)	3 (12%)	P > A > G
Patients with volume ≧ 0.75 ml/kg	2 (8%)	6 (12%)	1 (4%)	P = A = G

Abbreviations as in Table 1.

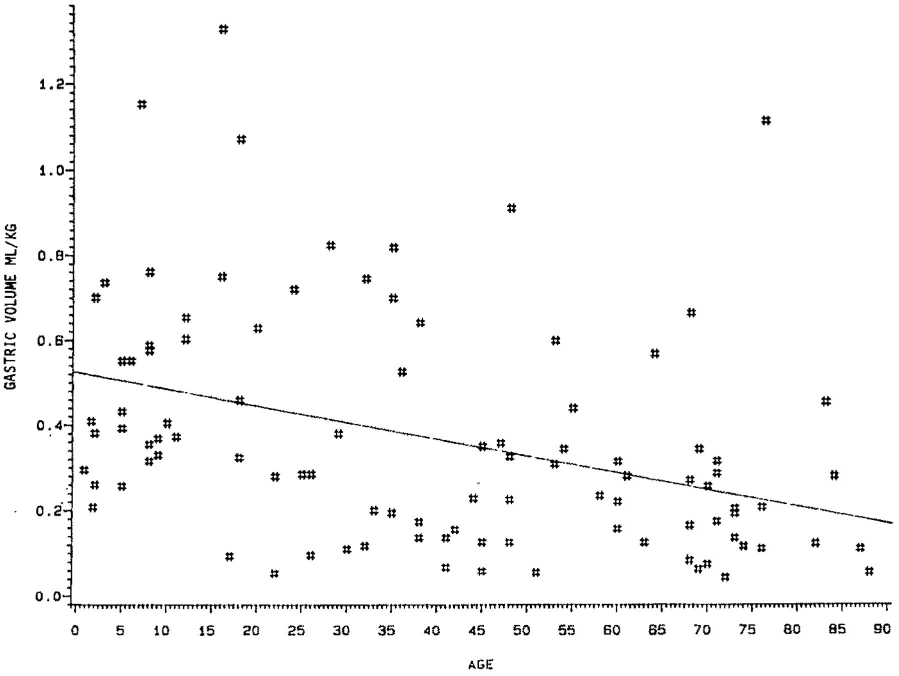

Figure 2. Relationship of gastric volume to age. Polynomial regression of gastric volume and body weight ratio, showing decreasing gastric volume with increasing age.

ml/kg. The proportions of patients with volumes ≧ 0.75 ml/kg did not differ significantly in the three groups.

Combined Risk of pH and Volume

The proportion of patients with both gastric pH ≦ 2.5 and gastric volume ≧ 0.3 ml or ≧ 0.4 ml/kg differed significantly among the three groups ($P = 0.0001$) (Table 4). The proportions decreased from the pediatric group to the adult group and from the adult group to the geriatric group. These proportions decreased significantly for the adult and geriatric groups for gastric pH ≦ 2.5 and gastric volume ≧ 0.3 ml ($P < 0.05$); while for proportions with combination of pH ≦ 2.5 and volume ≧ 0.4 ml, proportions decreased significantly from pediatric to adult group only ($P < 0.05$), the adult group was not significantly different from the geriatric group. The proportion of patients in the geriatric group was significantly less than that in the pediatric group ($P < 0.05$).

Relationship of Gastric Contents to Fasting Period

There was a significant linear relationship between gastric pH and length of fasting period for the three groups combined ($P = 0.0207$), indicating that as length of fasting period increased, pH decreased (Fig. 3).

Table 4. Frequency of Patients with Potential Risk Factors

	Pediatric age group	Adult age group	Geriatric age group	Directions and significance of difference
Patients with pH ≦ 2.50	23 (92%)	38 (76%)	15 (60%)	P = A; A = G; P > G
Patients with volume ≧ 0.3 ml/kg	21 (84%)	24 (48%)	5 (20%)	P > A > G
Combination of pH ≦ 2.5 and volume ≧ 0.3 ml/kg	20 (80%)	22 (44%)	5 (20%)	P > A > G
Patients with volume ≧ 0.4 ml/kg	15 (60%)	16 (32%)	3 (12%)	P > A > G
Combination of pH ≦ 2.5 and volume ≧ 0.4 ml/kg	15 (60%)	14 (28%)	3 (12%)	P > A = G

Abbreviations as in Table 1.

There was no significant correlation between gastric volume and length of fasting period in any of the three groups of patients (Fig. 4).

Discussion

Retrospective studies have shown that 26% of documented cases of pulmonary aspiration of gastric contents can be accounted for by general anesthesia and that mortality after aspiration of gastric contents can be as high as 60% (15,16). Even though pulmonary aspiration has been considered a potential risk if patients have 0.3–0.4 ml/kg of gastric contents at a pH below 2.5, aspiration pneumonitis has been reported after inhalation of gastric fluid with pH > 2.5 (17,18). Risk of serious pulmonary reaction increases progressively as the pH of aspirate decreases to < 2.5 (19).

In the present study, we have demonstrated that a potential risk of aspiration of acid gastric contents exists at all ages in inpatients undergoing elective surgery despite overnight fasting. A gastric pH ≦ 2.5 was seen in 76% of the patients in the three groups combined; the incidence was 92, 76, and 60% in the pediatric, adult, and geriatric age groups, respectively. Gastric volume ≧ 0.4 ml/kg were found in 35% of the patients in all three groups combined, while the incidence was 60, 32, and 12% in the pediatric, adult, and geriatric patients respectively. The proportions of patients with both pH ≦ 2.5 and volume ≧ 0.4 ml/kg were 60% for pediatric patients, 28% for adult patients, and 12% for geriatric patients. It was also demonstrated that the risk of acid aspiration decreased from the pediatric to the adult to the geriatric patients by the criteria of pH and volume. In addition, this investigation demonstrated linear relationships between age and gastric pH and between age and gastric volume, indicating that increasing age was related to an increase in pH and a decrease in gastric volume. Gastric acidity was found to increase with increased duration of fasting, but volume did not increase with increased duration of fasting.

The inability to determine precisely the location of the gastric tube used for sampling gastric contents is a limitation in this as in other comparable studies. There is the possibility of underestimation of volume of gastric contents, even though a standardized approach to aspirating gastric contents tends to minimize the importance of constant errors, as consistently higher gastric volumes were seen utilizing dye dilution techniques. Hence, we have analyzed risk factors independently and also analyzed gastric volume at these levels (0.1, 0.2, 0.3, 0.4, and 0.75 ml/kg).

Hester and Heath (4) demonstrated that there was no significant correlation between gastric pH or volume on the one hand and duration of fasting period (8–16 hr) on the other hand. However, Roberts and Shirley (3) showed, in patients having elective cesarean sections, that prolonged fasting (over 20 hr) was associated with greater mean gastric volumes than observed with shorter periods (12–16 hr) of fasting. In the present study, in contrast to both these reports, we found a correlation between duration of fasting and acidity of gastric contents, but we failed to demonstrate any correlation between volume and length of fasting period.

The results of this study and various other investigations show that a great number of patients, especially children and adults, are potentially at risk of pulmonary aspiration. Geriatric patients may seem to be at increased risk of regurgitation of gastric contents as frequency of hiatal hernia, gastroesophageal reflux and decrease in gastric motility increase with age (10–13). However, a decrease in gastric secretion by 50% by the age of 70 with no diminution in the lower esophageal sphincter tone (10–13) reduces the potential risk of pulmonary damage in normal patients. But older population may have altered lower esophageal

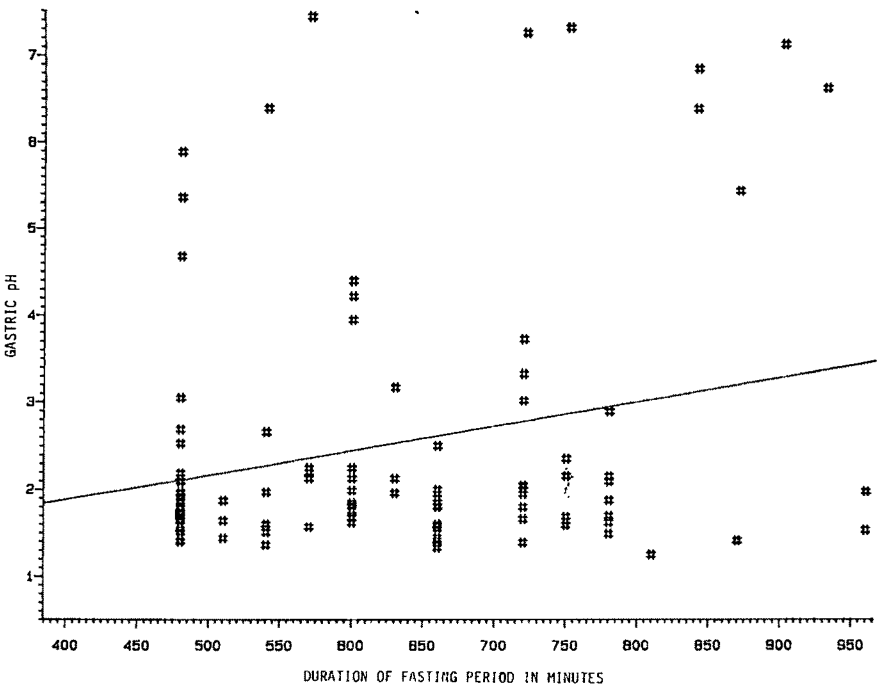

Figure 3. Relationship of duration of fasting period to gastric pH, indicating decrease in gastric pH as length of fasting period increased.

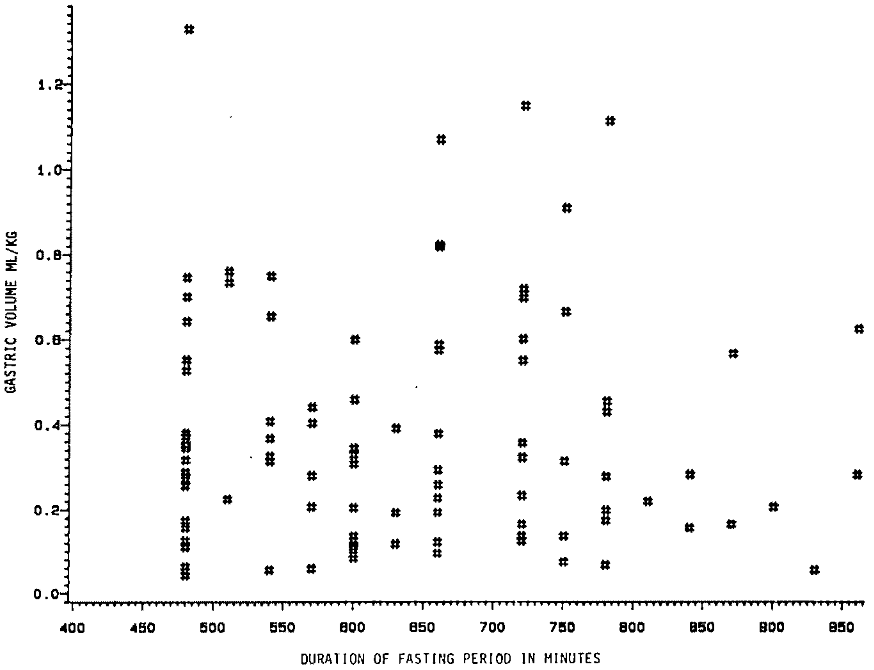

Figure 4. Relationship of length of fasting period to gastric volume, indicating no significant correlation between gastric volume (ml/kg) and length of fasting period.

sphincter tone and esophageal motility secondary to disorders such as diabetes mellitus, peripheral neuropathy, Parkinsonism, multiple sclerosis, and the anticholinergic effects of drugs used for the treatment of other conditions. Patients with gastrointestinal disorders, obese individuals, term parturients, and patients presenting for emergency surgery face an increased risk of aspiration pneumonitis. Hence, it seems reasonable to conclude that, theoretically, most patients undergoing surgery under general anesthesia should receive prophylactic therapy to reduce gastric volumes and acidity or increase lower esophageal sphincter tone, or both. The efficacy of various drugs to modify acid aspiration risk factors is highly variable. Presently, however, cimetidine, ranitidine, metoclopramide, and sodium citrate appear most reliable (6,8,9,20–22). Patients undergoing emergency, as well as elective, surgery may benefit by the preanesthetic administration of an H_2-receptor antagonist, a gastrokinetic agent, an antacid, or a combination of an H_2-receptor antagonist and metoclopramide or sodium citrate.

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1985;64:18–22

Enflurane and Adenosine 3′,5′-Cyclic Monophosphate Metabolism in Pancreatic Islets

Robin B. L. Ewart, MD, PhD, Ben F. Rusy, MD, and Mark W. Bradford, MD

EWART RBL, RUSY BF, BRADFORD MW. Enflurane and adenosine 3′,5′-cyclic monophosphate metabolism in pancreatic islets. Anesth Analg 1985;64:18–22.

The effects of enflurane at a concentration of 4% by volume in the gas phase upon rates of insulin secretion were correlated with islet contents of adenosine 3′,5′-cyclic monophosphate (cyclic AMP). At this concentration, enflurane was without effect upon the basal rate of insulin release in the presence of 2 mM glucose. By contrast, the anesthetic led to 84 and 86% inhibitions, respectively, of rates of insulin secretion stimulated by 20 mM glucose and 20 mM glucose plus 1 mM theophylline. Enflurane also led to small reductions in islet cyclic AMP content under all conditions of incubation, and a statistically significant ($P < 0.02$) effect of the anesthetic in lowering cyclic AMP content was seen in islets exposed to 20 mM glucose plus 1 mM theophylline. Enflurane was without effect upon the activity of the low K_m cyclic AMP phosphodiesterase of the islet under the conditions employed. By contrast, the anesthetic led to significant inhibitions of both basal and fluoride-stimulated islet adenylate cyclase activity (34%, $P < 0.01$ and 23%, $P < 0.005$, respectively). It is concluded that under the conditions employed, enflurane leads to inhibition of islet adenylate cyclase activity and to small resultant reductions in islet cyclic AMP content. These effects appear to be of insufficient magnitude to explain completely the observed degree of insulin secretory inhibition by the anesthetic.

Key Words: HORMONES—insulin. ANESTHETICS, VOLATILE—enflurane.

We have previously demonstrated that enflurane, in the range of concentrations employed clinically, leads to a significant concentration-dependent inhibition of glucose-stimulated insulin secretion by isolated rat pancreatic islets of Langerhans without associated inhibition of islet glucose metabolism or protein biosynthesis (1). Adenosine 3′,5′-cyclic monophosphate (cyclic AMP) is known to fulfill a permissive role in the regulation of rates of glucose-stimulated insulin secretion and to augment the effects of submaximally stimulating concentrations of other insulin secretagogues (2). Because volatile anesthetics have been shown to affect cyclic AMP metabolism in a variety of tissues (3–6), it seemed possible that the observed inhibition of islet insulin secretion by enflurane might be explained by reduction in islet cyclic AMP concentration. The present studies were undertaken to examine the effects of enflurane upon islet cyclic AMP concentrations and upon the activities of islet adenylate cyclase and cyclic AMP phosphodiesterase.

Methods

Materials

Bovine plasma albumin (fraction V), theophylline, ATP, cyclic AMP, EDTA, Trizma base, creatine phosphate, creatine phosphokinase (Type I, 50–150 units/mg), 5′-nucleotidase, QAE-Sephadex, and sodium fluoride were obtained from Sigma Chemical Company (St. Louis, MO). New England Nuclear Corporation (Boston, MA) supplied [α-^{32}P] ATP of specific radioactivity in the range of 300 Ci/mM. Cyclic AMP assay kits and [8-^{3}H] cyclic AMP were purchased from Amersham (Arlington Heights, IL). Neutral alumina (activity I) was from Brinkmann Instruments (Canada). Enflurane and an enflurane vaporizer were obtained from Ohio Medical Products (Madison, WI). Other chemicals were of the highest purity available from commercial sources.

Preparation of Islets

Islets of Langerhans were isolated by the collagenase-digestion technique of Lacy and Kostianovsky (7) from

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Address correspondence to Dr. Ewart, Chief of Medical Service, Veterans Administration Medical Center, 800 Zorn Avenue, Louisville, KY 40202.

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pancreases obtained from 200- to 250-g male Sprague–Dawley rats fed ad libitum.

Insulin Release and Determination of Islet Cyclic AMP Content

Groups of 20 islets were incubated in 50 μl-volumes of a bicarbonate buffered salt solution (8) containing 1 mg/ml of bovine plasma albumin and 2 mM Ca^{2+} together with 2 mM glucose, 20 mM glucose, or 20 mM glucose with 1 mM theophylline. Control incubations were equilibrated with O_2:CO_2 (95:5, vol/vol) and experimental incubations with the same gas mixture containing 4% (vol/vol) enflurane as described previously (1). At the conclusion of the 30-min period of incubation, samples of 4 μl of the media were taken and diluted to 400 μl for assay of their insulin contents by a double-antibody radioimmunoassay based on the method of Hales and Randle (9). For determination of islet cyclic AMP content, 54 μl-volumes of 50 mM Tris-HCl buffer (pH 7.5) containing 8 mM disodium EDTA were then added to each incubation vial, the vial contents were sonicated for 10 sec at setting 1.5 of an Ultrasonic sonicator (Ultrasonics, Inc., Plainview, NY), and the vials were transferred immediately to a boiling water bath for 5 min to precipitate protein. Vials were gassed continuously with the appropriate gas mixture during the sampling and sonication procedures to ensure that the concentration of enflurane in the liquid phase did not fall before heat inactivation of cyclic nucleotide metabolism had occurred. Precipitated protein was then separated by centrifugation at 1200 × *g* for 5 min and 90 μl aliquots of the supernatant were retained for cyclic AMP determination by the competitive protein binding assay of Brown et al. (10).

Determination of Islet Cyclic AMP Phosphodiesterase

The enzyme was prepared by homogenizing 200 islets in 1 ml of 50 mM Tris-HCl buffer (pH 7.5). Nuclei and cell debris were removed by centrifugation at 600 × *g* for 5 min and the supernatant was stored at −20°C until use. Cyclic AMP phosphodiesterase activity was determined by a modification of the method of Sugden et al. (11). The reaction mixture, of final volume 100 μl, contained 50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 50 μM $CaCl_2$ and 1 μM cyclic [^{3}H] AMP (approximately 10^5 disintegrations per min). The reaction was initiated by the addition of 25 μl of the enzyme and incubation was continued at 37°C for 10 min under an atmosphere of air or air containing enflurane (4%, vol/vol). Under the conditions employed, the reaction was shown to proceed linearly with time for up to 20 min with less than 25% of substrate consumed. After the enzyme was inactivated by boiling for 5 min, the primary product of the reaction, 5′-AMP, was converted to adenosine by the addition of 250 mU of snake venom 5′-nucleotidase followed by incubation at 37°C for 15 min. The secondary reaction product, adenosine, was separated from the unhydrolyzed cyclic AMP by chromatography on 6 × 0.5 cm columns of QAE-Sephadex (chloride form). The radioactivity of the eluted adenosine was quantitated by liquid scintillation counting at an efficiency of 28%, employing a Packard Tri-Carb liquid scintillation spectrometer.

Determination of Islet Adenylate Cyclase

Islet adenylate cyclase was determined by measuring the rate of conversion of [α-^{32}P] ATP to cyclic [^{32}P] AMP using the method of Pohl et al. (12). The enzyme was prepared by homogenizing 400 islets in 400 μl of 50 mM Tris-HCl buffer (pH 7.5) using six passes of an all-glass homogenizer (Kontes Glass Co., Vineland, NJ). The homogenate was maintained in an ice bath and aliquots of 25 μl were employed in the assay within 15 min of their preparation. The final assay mixture, of total volume 100 μl, contained 50 mM Tris-HCl buffer (pH 7.5), 5 mM $MgCl_2$, 1 mM EDTA, 10 mM theophylline, 100 μM [α-^{32}P] ATP (approximately 2 × 10^6 disintegrations per min) and an ATP-regenerating system consisting of 25 mM creatine phosphate and 1 mg/ml creatine phosphokinase. After adding the enzyme to start the reaction, it was allowed to proceed at 37°C for 10 min under an atmosphere of air or air containing enflurane (4%, vol/vol) when it was terminated by addition of 100 μl of a stopping mixture containing 50 mM Tris-HCl buffer (pH 7.5), 40 mM ATP, 12.5 mM cyclic AMP, 10 mg/ml of sodium lauryl sulphate, and 59 nCi of cyclic [^{3}H] AMP to act as a recovery marker in the subsequent separation procedure employing 4 × 1.6 cm columns of neutral alumina as described by Ramachandran (13). The eluted cyclic [^{32}P] AMP was determined by liquid scintillation counting and correction was made for column losses as described by Pohl et al. (12). Under the conditions of the assay, adenylate cyclase activity proceeded as a linear function of time and enzyme concentration for at least 15 min.

Determination of Enflurane Concentration

In all experiments, an enflurane concentration of 4% by volume in the gas phase was employed. The concentration of enflurane in the liquid phase in equilib-

Table 1. Effects of Enflurane on Islet Cyclic AMP Content and Rates of Insulin Secretion

	Rate of insulin release (μU·20 islets^{-1}·30 min^{-1})		Islet cyclic AMP content (fmol/20 islets)	
Additions to medium	No enflurane	Enflurane (4%, vol/vol)	No enflurane	Enflurane (4%, vol/vol)
Glucose (2 mM)	92 ± 6	87 ± 3	120 ± 8	102 ± 18
Glucose (20 mM)	625 ± 75[a]	102 ± 13[b]	188 ± 23[c]	169 ± 7
Glucose (20 mM) plus theophylline (1 mM)	1175 ± 81[a,b]	167 ± 30	276 ± 17[a,d]	226 ± 7[e]

Results are mean ± SEM of at least six observations.
[a] $P < 0.001$ when compared to 2 mM glucose, no enflurane.
[b] $P < 0.001$ when compared to 20 mM glucose, no enflurane.
[c] $P < 0.02$ when compared to 2 mM glucose, no enflurane.
[d] $P < 0.02$ when compared to 20 mM glucose, no enflurane.
[e] $P < 0.02$ when compared to 20 mM glucose plus 1 mM theophylline, no enflurane.

rium with enflurane (4%, vol/vol) in the gas phase was determined to be equivalent to 1.26 mM by a gas chromatographic technique described previously (1).

Statistical Analysis of Results

Results are expressed throughout in terms of the mean ± SEM. Levels of statistical significance between control and experimental means were determined by calculation of t values.

Results

Effects of Enflurane on Islet Insulin Release and Cyclic AMP Content

The effects of enflurane (4%, vol/vol) on the observed rate of insulin release and cyclic AMP concentration seen in the presence of a nonstimulating glucose concentration (2 mM), a maximally stimulating glucose concentration (20 mM), and a maximally stimulating glucose concentration (20 mM) together with a known inhibitor of phosphodiesterase (1 mM theophylline), are shown in Table 1. The effect of increasing glucose concentration on the rate of insulin release is clearly shown with the rate in the presence of 20 mM glucose as being 679% of that observed in the presence of 2 mM glucose ($P < 0.001$). The addition of 1 mM theophylline to the medium containing 20 mM glucose led to an 88% further increase in the rate of insulin release ($P < 0.001$). As shown in Table 1, enflurane had no effect on basal rates of insulin secretion in the presence of 2 mM glucose, but the anesthetic led to an 84% reduction in the rate of insulin release in the presence of 20 mM glucose ($P < 0.001$). Addition of 1 mM theophylline to the 20 mM glucose medium did not lead to a statistically significant increase in the rate of insulin release in the presence of 4% enflurane by volume (Table 1). Thus the extent of enflurane inhibition in the presence of simultaneous islet stimulation by 20 mM glucose and 1 mM theophylline was 86%, essentially identical to that seen in the presence of 20 mM glucose alone.

As shown in Table 1, islet cyclic AMP content increased significantly in the presence of 20 mM glucose when compared to the content determined in islets exposed to a nonstimulating glucose concentration of 2 mM ($P < 0.02$). Addition of 1 mM theophylline led to a further 47% increase in the islet content of cyclic AMP over that seen in the case of islets incubated with 20 mM glucose alone ($P < 0.02$).

Enflurane led to reductions in islet cyclic AMP content that achieved statistical significance in the case of islets exposed to 20 mM glucose together with 1 mM theophylline ($P < 0.02$). In addition, in a series of 21 pairs of observations, in only two cases were equal or higher cyclic AMP concentrations seen in the presence of enflurane (4%, vol/vol) than in the corresponding controls, irrespective of the other additions to the medium.

Effects of Enflurane on Islet Cyclic AMP Phosphodiesterase and Adenylate Cyclase

Because the preceding results suggested that the inhibition of insulin secretion seen in the presence of enflurane could in part be due to an alteration in cyclic AMP metabolism, the activities of the enzymes responsible for the formation and the degradation of cyclic AMP were determined under the conditions shown in Table 2. Enflurane had no effect on the activity of islet cyclic AMP phosphodiesterase, while theophylline, employed as a positive control at concentrations of 5×10^{-5} M and 5×10^{-4} M, led to 13 and 62% reductions in enzyme activity when compared to control ($P < 0.01$ and $P < 0.001$, respectively). By contrast, as shown in Table 2, the anes-

Table 2. Effects of Enflurane on Islet Cyclic AMP Phosphodiesterase (PDE) and Adenylate Cyclase

Additions to medium	Cyclic AMP PDE activity (Cyclic AMP hydrolyzed pmol·5 islets^{-1}·30 min^{-1})	Adenylate cyclase activity (Cyclic [^{32}P]AMP formed pmol·25 islets^{-1}·30 min^{-1})
None (control)	14.92 ± 0.07	6.67 ± 0.38
Enflurane (4%, vol/vol)	14.87 ± 0.06	4.41 ± 0.56^{a}
Theophylline 5 × 10^{-5} M	13.03 ± 0.54^{a}	—
Theophylline 5 × 10^{-4} M	5.72 ± 0.32^{b}	—
NaF	—	13.40 ± 0.63
NaF plus enflurane (4%, vol/vol)	—	10.34 ± 0.65^{c}

Values shown are mean ± SEM of at least six observations.
[a] $P < 0.01$ when compared to control.
[b] $P < 0.001$ when compared to control.
[c] $P < 0.005$ when compared to NaF.

thetic led to a 34% reduction in islet adenylate cyclase activity when compared to control ($P < 0.01$). Addition of 10 mM NaF, a known stimulator of adenylate cyclase, increased the activity of the enzyme to 201% of control. In the presence of 10 mM NaF, enflurane led to a 23% reduction ($P < 0.005$) in the activity of the islet adenylate cyclase (Table 2).

Discussion

The mechanism by which glucose stimulates insulin release from pancreatic islets of Langerhans is incompletely understood. It has generally been assumed that glucose or one of its metabolites interacting with cyclic AMP, extracellular and intracellular cations, and the microfilaments and microtubules of the islet cells, leads to fusion of the membranes of the insulin-containing secretory granules with the plasma membrane of the cells, with resultant release of stored insulin. Any hypothesis explaining insulin secretion must incorporate cyclic AMP, the adenylate cyclase system, and cyclic nucleotide phosphodiesterase because it is known that glucose and other secretagogues increase the intracellular content of cyclic AMP and that cyclic AMP potentiates the insulin-releasing action of glucose (2).

In the experiments reported here, glucose significantly increased the islet content of cyclic AMP. Theophylline, a known inhibitor of cyclic AMP phosphodiesterase, further increased the islet content of the cyclic nucleotide and potentiated the insulin release seen in the presence of maximally stimulating glucose concentration (Table 1).

Because we have previously shown a concentration-dependent inhibition of insulin release by enflurane with almost complete inhibition of secretion of the hormone at an enflurane concentration of 4% by volume (1), this concentration of the anesthetic was employed to determine whether it exerted an effect on islet cyclic AMP metabolism in the experiments described here. In the present studies, the inhibitory effect of enflurane upon insulin release was confirmed. Although islet cyclic AMP levels were uniformly lowered by enflurane, the decrease observed achieved statistical significance only in the case of islets exposed to a stimulatory glucose concentration (20 mM) in the presence of 1 mM theophylline (Table 1). Furthermore, the extent of decline in islet cyclic AMP content seen under even the most favorable conditions (18%) greatly contrasted the dramatic inhibition of insulin release observed (86%) and suggests that although enflurane does reduce islet cyclic AMP content, this cannot be the major mechanism explaining the inhibition of insulin release by the anesthetic. Furthermore, it is clear from the data presented that even the striking increase in islet cyclic AMP content caused by 1 mM theophylline did not reverse the enflurane-induced inhibition of insulin secretion (Table 1).

Despite these considerations, it seemed of interest to determine the mechanism by which enflurane alters the islet content of cyclic AMP. For this reason, the effects of the anesthetic upon the activities of the islet enzymes responsible for the formation and the degradation of cyclic AMP were examined. Islets are known to contain two cyclic AMP phosphodiesterase activities with apparent K_m values for cyclic AMP of 3 μM and 30 μM (14). The islet concentration of cyclic AMP is generally accepted to be approximately 1 μM (14), which our present results support. Thus assuming an islet wet weight of approximately 10 μg, the cyclic AMP contents reported in Table 1 correspond to islet concentrations of the cyclic nucleotide of 0.6, 0.94, and 1.38 μM in the presence of 2 mM glucose, 20 mM glucose, and 20 mM glucose plus 1 mM theophylline, respectively. Because the apparent K_m value of the low-K_m phosphodiesterase closely approximates the islet concentration of the cyclic nucleotide, this form of the enzyme is thought to be the major physiological determinant of rates of cyclic AMP degradation. In the present studies, enflurane was without effect upon the observed rate of cyclic AMP hydrolysis by the low-K_m enzyme in experiments employing a substrate concentration of 1 μM (Table 2). By contrast, enflurane led to statistically significant inhibitions of both basal and NaF-stimulated adenylate cyclase activities of the islet cells (Table 2), thus providing an explanation for the reduced islet cyclic AMP contents observed.

The effects of volatile anesthetics on cyclic AMP metabolism have been studied in a variety of rat tissues. In the rat caudate nucleus, enflurane in concentrations of 3 and 5% by volume in the gas phase increased adenylate cyclase activity by 11 and 22%, respectively, above basal levels (3). In the same report, enflurane at 5% by volume also decreased the activity of the low-K_m form of cyclic AMP phosphodiesterase by 24%. In contrast, in rat uterine muscle, halothane has been shown to increase the activities of both adenylate cyclase and phosphodiesterase in a dose-dependent fashion (4). These effects led to increased cyclic AMP levels, owing to a greater increase in the activity of adenylate cyclase than of phosphodiesterase in this tissue. In contrast to our findings in islets, halothane has been shown to enhance the stimulation of uterine muscle adenylate cyclase by NaF, a finding that has been interpreted as supporting an action of halothane on the catalytic unit of the enzyme (15). It appears that the volatile anesthetics display tissue specificity in terms of their effects upon cyclic AMP metabolism. Thus the results presented here relating to anesthetic effects upon islet cyclic AMP metabolism differ from those previously reported for nonislet tissue in the rat.

In conclusion, enflurane (4%, vol/vol) significantly inhibits islet adenylate cyclase without altering the activity of the low-K_m cyclic AMP phosphodiesterase, thus leading to minor reductions in islet cyclic AMP content. However, the dramatic inhibition of insulin release seen in response to this concentration of enflurane cannot be attributed solely to reduction in islet cyclic AMP concentration. First, the reduction of cyclic AMP concentration observed does not appear to be of sufficient magnitude and, second, elevation of islet cyclic AMP concentration by theophylline does not reverse the insulin-secretory inhibition exerted by the anesthetic. Studies are proceeding in our laboratory to elucidate further the nature of the inhibition of insulin release by enflurane.

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Pharmacokinetics and Pharmacodynamics of *d*-Tubocurarine and Metocurine in the Elderly

Richard S. Matteo, MD, Walter W. Backus, MD, Dudley D. McDaniel, MD, William P. Brotherton, MD, Robin Abraham, MS, and Jaime Diaz

MATTEO RS, BACKUS WW, McDANIEL DD, BROTHERTON WP, ABRAHAM R, DIAZ J. Pharmacokinetics and pharmacodynamics of *d*-tubocurarine and metocurine in the elderly. Anesth Analg 1985;64:23–9.

The effects of age (older than 70 yr) on the pharmacokinetics and pharmacodynamics of d-tubocurarine (dTc) and metocurine (MTc) were evaluated in studies of 21 patients aged 70–87 and 21 patients aged 29–59. There was a significant difference in the pharmacokinetic parameters of all elderly patients compared with younger controls. With both dTc and MTc, the elderly exhibited a decreased plasma clearance, decreased initial volume of distribution, decreased volume of distribution, and a prolonged elimination half-life. After 0.3 mg/kg of dTc, the times for 50% return of twitch and recovery index (25–75% return of twitch response) in the elderly were significantly longer than in the young (P < 0.02). A similar observation was made for the elderly patients receiving 0.15 mg/kg of MTc. No significant difference was seen in the log plasma concentration–twitch response relationship between 20–80% paralysis in young and in elderly patients receiving dTc. There was a similar lack of significant difference between the log plasma concentration–twitch response lines for elderly and young patients receiving MTc. Because there was no difference between the plasma concentration–response relationships in the elderly and young, altered sensitivity to dTc or MTc cannot explain the longer duration of action seen in the elderly. The most likely explanation for this difference is the altered pharmacokinetics of these two drugs in the elderly.

Key Words: NEUROMUSCULAR RELAXANTS—*d*-tubocurarine, metocurine. PHARMACOKINETICS—*d*-tubocurarine, metocurine. PHARMACODYNAMICS—*d*-tubocurarine, metocurine.

It has been well established that the pharmacokinetics of numerous drugs in the elderly differ from those in young patients (1–4). These differences are in large part a result of the normal aging process. In elderly patients, decreased total body fluid, decreased lean body mass with relative increase in body fat, and decrease serum albumin with decreased protein binding can alter drug distribution. In addition, decreased cardiac output, reduced splanchnic blood flow with slow delivery of drug to the liver, and decreased kidney function, as evidenced by decreased renal blood flow, decreased glomerular filtration rate, and decreased transport maximum can profoundly alter elimination of drugs. There is also considerable evidence that differences in the distribution and elimination of drugs may account in large part for the increase in adverse drug reactions in aged patients (1–4).

Significant differences in the pharmacokinetics and pharmacodynamics of muscle relaxants in elderly patients compared with younger controls has been reported for pancuronium (5,6), alcuronium (7), and vecuronium (8,9). This study was undertaken to determine the distribution, elimination, and actions of *d*-tubocurarine (*d*Tc) and metocurine (MTc) in elderly patients (older than 70 yr).

Methods

Twenty-one elderly neurosurgical patients (70–87 yr) and 21 younger adults (29–59 yr) undergoing craniotomy for brain tumor or carotid endarterectomy were studied, after obtaining institutional approval and informed consent. All patients' motoneuron systems were intact, and serum creatinine and BUN levels were within normal limits. The duration of the surgical procedure ranged from 3 to 9 hr. Kinetics and dynamics were studied simultaneously in all 14 pa-

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Address correspondence to Dr. Matteo, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, New York 10032.

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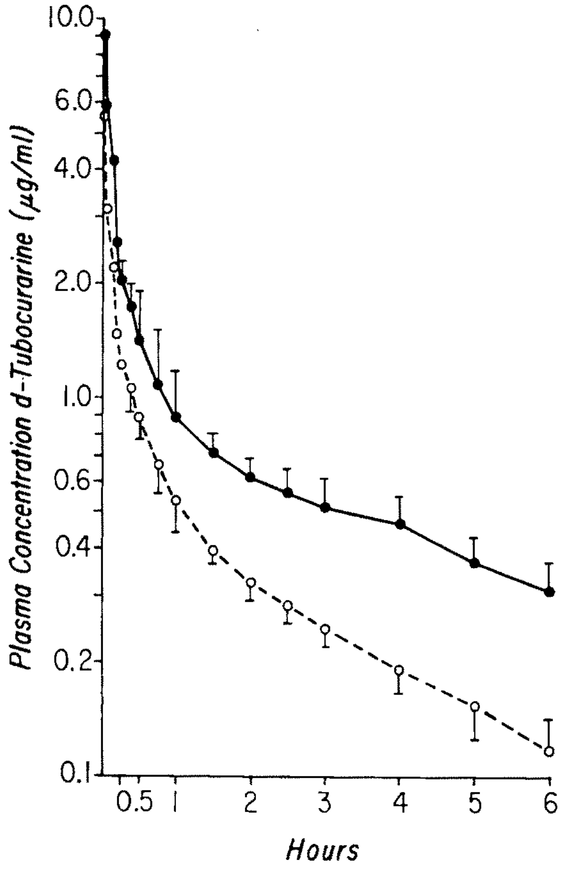

Figure 1. Plasma concentration–time course curves for elderly (●——●) and younger controls (○—○) after a single intravenous dose (0.3 mg/kg) of *d*Tc. Time is from 0 to 6 hr. Values are means ± SD, *n* = 7 in both groups.

tients receiving 0.3 mg/kg of dTc. The pharmacokinetics of metocurine were studied in 14 patients who received 0.3 mg/kg of MTc. The dynamics of metocurine were separately studied in another group of 14 patients who received 0.15 mg/kg of MTc.

Premedication in most cases consisted of secobarbital (50–120 mg) and atropine (0.3–0.5 mg), though 4 of the elderly received atropine alone. The dose was based on the clinical judgment of the patient's anesthesiologist. Every patient was given an intravenous infusion of 500–800 ml lactated Ringer's solution before induction of anesthesia. Also prior to induction of anesthesia, an arterial catheter was placed in the patient's radial artery. Anesthesia was induced with thiopental (175–300 mg), the trachea intubated with the aid of succinylcholine (1 mg/kg), and anesthesia maintained with nitrous oxide–oxygen (60–40%) and halothane (0.4–0.9%), inspired. The anesthetic concentration in each patient remained constant throughout the study. Mechanical ventilation was maintained with moderate hyperventilation (Pa_{CO_2} 25–35 mm Hg) and core temperature was maintained in all patients between 35.8 and 37.1°C with the aid of warming blankets. Throughout the anesthesia and surgical procedure, all patients received intravenous fluids, which consisted of Ringer's solution or Normosol (Abbott) and 5% dextrose in water at a rate of 3–4 $ml\cdot kg^{-1}\cdot hr^{-1}$. They also received oxacillin, dexamethasone, and, when indicated during vascular surgery, heparin.

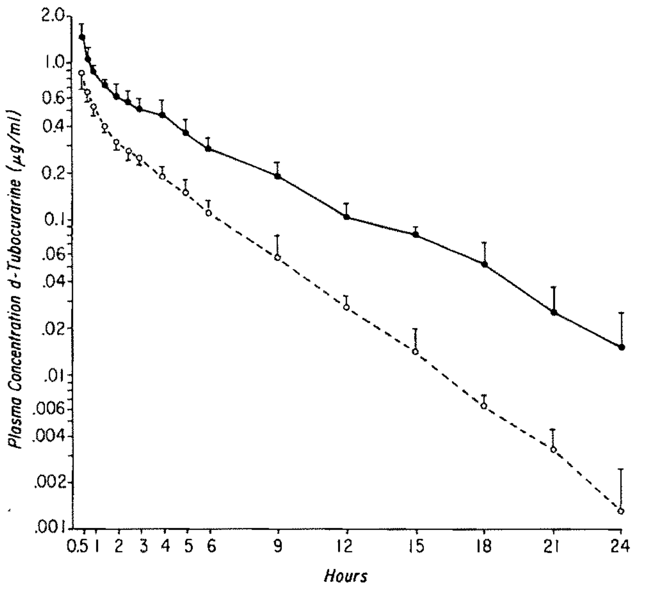

Figure 2. Plasma concentration–time course curves for elderly (●——●) and younger controls (○—○) after a single intravenous dose (0.3 mg/kg) of *d*Tc. Time is from 0.5 to 24 hr. Values are mean ± SD, *n* = 7 in both groups. Values between 12 and 24 hr were not always drawn at precisely 3-hr intervals, and in these cases the plasma concentrations for the proper times were derived from the patient's individual exponential equation.

After induction of anesthesia, a forearm and hand of each patient were firmly fixed to a metal armboard, and the thumb was adducted in a yoke connected to a Grass force displacement transducer (FT-10) to measure twitch tension. The ulnar nerve was stimulated at the wrist with subcutaneous needle electrodes with supramaximal stimuli from a Grass stimulator (Model S-8) in conjunction with a Grass stimulus isolation unit. The responses to a single stimuli of 0.2 msec duration delivered at a frequency of 0.1 Hz (6 stimuli/min) were observed. In addition, a tetanus of 50 Hz was used to make sure no residual effects of succinylcholine were present (phase II block). After this, a stable baseline of twitch tension was recorded for 10 min.

At this point, patients in whom pharmacokinetics were studied were given a single dose of either *d*Tc (0.3 mg/kg) or MTc (0.3 mg/kg). Blood samples were obtained from the arterial catheter in heparinized tubes

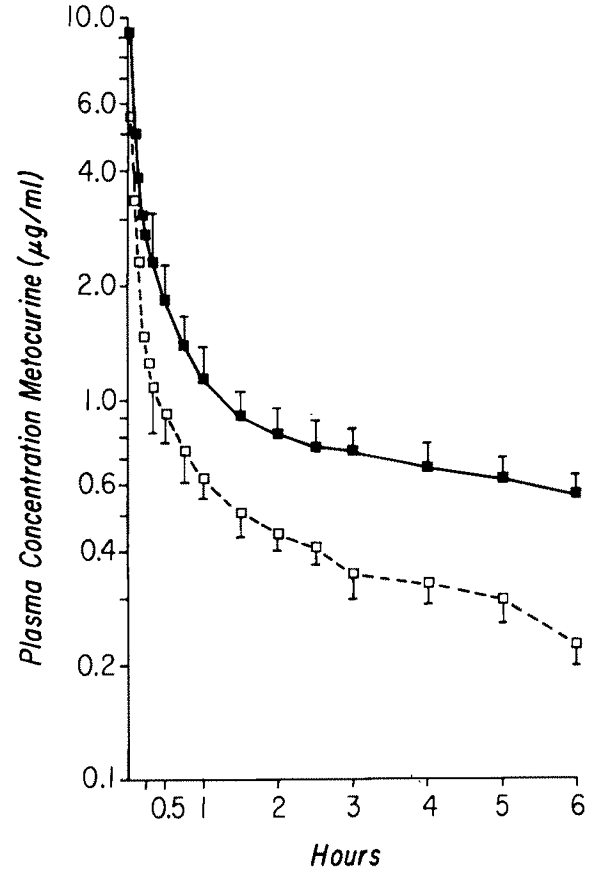

Figure 3. Plasma concentration–time course curves for elderly (■——■) and younger controls (□—□) after a single intravenous dose (0.3 mg/kg) of metocurine. Time from 0 to 6 hr. Values are means ± SD, $n = 7$ in both groups.

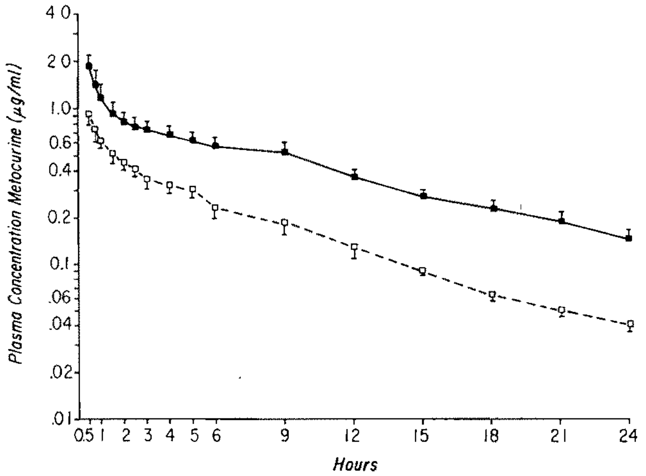

Figure 4. Plasma concentration–time course curves for elderly (■——■) and younger controls (□—□) after a single intravenous dose (0.3 mg/kg) of metocurine. Time from 0.5 to 24 hr. Values are means ± SD, $n = 7$ for both groups. Values between 12 and 24 hr were not always drawn at precisely 3-hr intervals, and in those cases the plasma concentrations for the proper time were derived from the patient's individual exponential equation.

at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150 min; and at 3, 4, 5, 6, 9 hr; between 12 and 24 hr either 3 or 4 samples were drawn with at least 2 hr between each sample. Volume of each blood sample was 1 ml.

In the *d*Tc study, dynamics were studied simultaneously with kinetics, and additional samples were drawn between the timed kinetic samples, if return of twitch warranted obtaining another sample. The pharmacodynamics of metocurine were studied in another group of 14 patients, whose twitch was monitored as described previously, but who received a single dose of 0.15 mg/kg of MTc. This dose of MTc was chosen to serve as the equivalent to a dose of 0.3 mg/kg of dTc. Again, as twitch returned, blood samples were obtained, heparinized, the plasma separated and frozen until analyzed for *d*Tc by the radioimmunoassay method of Horowitz and Spector (10) or the modification of this method for MTc (11).

In analyzing the kinetic data, plasma concentration–time data from each patient who received either *d*TC or MTc were fitted to both a 2- and 3-compartment open model using a weighted nonlinear least squares regression program. The method described by Boxenbaum et al. (12) was employed to determine which model best described the data.

The plasma clearance (Clp), half-life of elimination ($t_{1/2}$ elim), initial volume of distribution (V_p), and volume of distribution (Vd_{area}), were calculated from the coefficients and exponents of the derived polyexponential equation by the methods described by Wagner (13). Comparisons between the pharmacokinetic parameters of the elderly and their younger controls who received either *d*Tc or MTc were made by applying Student's *t*-test for unpaired data (two-tailed).

In analyzing the pharmacodynamic data, the log plasma concentration–response curves were constructed for the linear portion of the plasma concentration–response curves between 20–80% paralysis for each patient (14). The complete sigmoid concentration–response curves could not be determined, because the twitch response in many of the elderly patients had not returned to control levels by the end of surgery. In every patient, however, the twitch had returned to at least 75% of the control value. The measured concentration–response points for the elderly and their younger controls receiving either *d*Tc or MTc were compared by analysis of covariance. The times required for recovery of twitch tension from 25 to 75% of control value (recovery index) and times to 50% recovery were recorded for the elderly and younger controls for each drug. Statistical significance was

Table 1. *d*-Tubocurarine Pharmacokinetic Parameters (Mean ± SD)

	Elderly, $n = 7$ (70–87 yr)	Young controls, $n = 7$ (30–56 yr)	P
$t_{1/2}$ elim (min)	268 ± 51	173 ± 38	<0.05
Clp (ml·kg^{-1}·min^{-1})	0.79 ± 0.18	1.71 ± 0.32	<0.025
V_p (L/kg)	0.025 ± 0.006	0.038 ± 0.007	<0.025
Vd_{area} (L/kg)	0.281 ± 0.04	0.425 ± 0.06	<0.01

Table 2. Metocurine Pharmacokinetic Parameters (Mean ± SD)

	Elderly, $n = 7$ (70–81 yr)	Young controls, $n = 7$ (29–52 yr)	P
$t_{1/2}$ elim (min)	530 ± 83	269 ± 56	<0.025
Clp (ml·kg^{-1}·min^{-1})	0.36 ± 0.08	1.1 ± 0.16	<0.01
V_p (L/kg)	0.021 ± 0.008	0.039 ± 0.009	<0.01
Vd_{area} (L/kg)	0.278 ± 0.034	0.446 ± 0.042	<0.01

determined by Student's *t*-test (two-tailed). $P < 0.05$ was considered significant.

Results

The plasma concentration–time course curves in patients receiving 0.3 mg/kg of *d*Tc to 6 hr are displayed in Figure 1 and to 24 hr in Figure 2. Similar curves for MTc to 6 hr and 24 hr are shown in Figures 3 and 4.

At each time point on the plasma decay curves, the elderly patients receiving both *d*Tc and MTc exhibited a significantly higher plasma concentration of the relaxant than the younger patients, the exception being that the mean plasma *d*Tc concentration of the elderly at 24 hr was greater than in the young, but the difference was not statistically significant.

Plasma decrement curves for all patients are best described by three-compartment models. The relationship between plasma concentration and time is described by the following equations: *d*Tc, elderly, $C = 8.65e^{-0.34t} + 2.21e^{-0.04t} + 0.849e^{-0.0028t}$; *d*Tc, younger controls, $C = 5.94e^{-0.48t} + 1.42e^{-0.04t} + 0.52e^{-0.0041t}$; MTc, elderly, $C = 10.5e^{-0.71t} + 3.2e^{-0.04t} + 0.92e^{-0.0013t}$; MTc, younger controls, $C = 5.75e^{-0.4t} + 1.18e^{-0.036t} + 0.55e^{-0.0029t}$, where C is concentration in μg/ml and t is time in min. The pharmacokinetic parameters for patients receiving *d*Tc are presented in Table 1, and for patients receiving MTc in Table 2. There are significant differences in the pharmacokinetic parameters of all the elderly patients, regardless of whether they received *d*Tc or MTc, when compared with the younger patients. The elderly exhibit a decreased plasma clearance, decreased initial volume of distribution, decreased volume of distribution, and a prolonged elimination half-life.

There was no significant difference seen in the log plasma concentration–twitch response relationship between 20–80% paralysis for the elderly and the younger patients receiving *d*Tc (Fig. 5). There was a similar lack of significant difference between the log plasma concentration–twitch response relationship for those patients receiving MTc (Fig. 6). After 0.3 mg/kg of *d*Tc, the time for 50% return of twitch and the recovery index was prolonged in the elderly (Table 3). Similarly, elderly patients receiving 0.15 mg/kg MTc also displayed a longer time to 50% return of twitch, and their recovery index was longer than in their controls (Table 4).

Discussion

Recent review articles have described changes in body composition and function accompanying the aging process that alter the distribution, elimination, and actions of drugs (1–4). Among the changes seen with increasing age are decreased lean body mass, relative increase in body fat, decreased total body fluid, decreased cardiac output, reduced splanchnic blood flow with slow delivery of drugs to liver, and decreased kidney function as a result of decreased renal blood flow, decreased glomerular filtration rate, and decreased transport maximum. The authors of all of these 4 review articles point out that these changes can account for many adverse drug reactions in the elderly. Triggs and Nation (1) have pointed out that the most common pharmacokinetic change reported in the literature is a prolonged drug half-life.

The long-acting muscle relaxants (pancuronium, *d*-tubocurarine, and metocurine) depend initially on redistribution and ultimately on urinary excretion for their elimination. Thus in elderly patients with decreased cell mass and reduced kidney function, these drugs might be expected to have a longer duration of action.

In our study, the recovery index was significantly prolonged in the elderly who received both *d*Tc and MTc. With both drugs the elderly patients exhibited a significantly decreased plasma clearance, a decreased initial volume of distribution (plasma volume), a decreased volume of distribution, and a prolonged elimination half-life. With both *d*Tc and MTc there was no difference between the plasma concentration–response relationships of the elderly and the

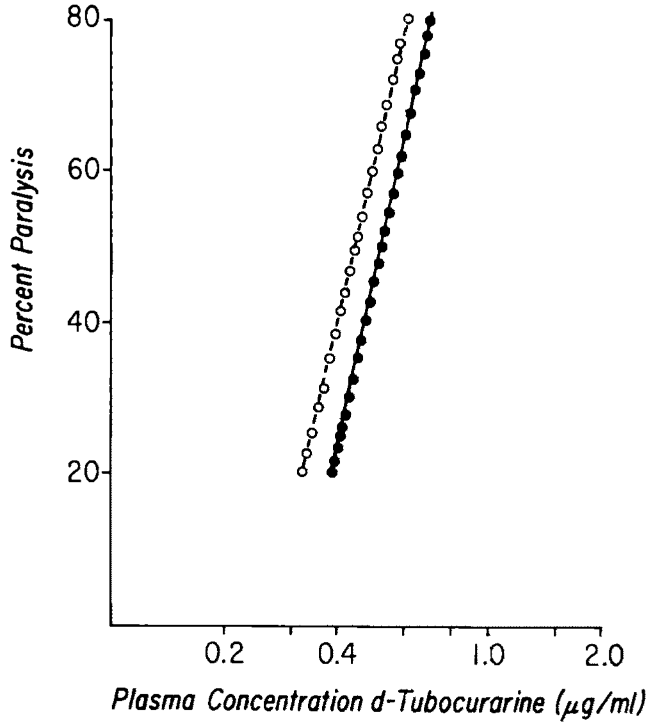

Figure 5. Regression lines for elderly (●——●) and younger controls (○—○) given 0.3 mg/kg of *d*Tc, log plasma concentration–response between 20 and 80% paralysis; $n = 7$ in both groups.

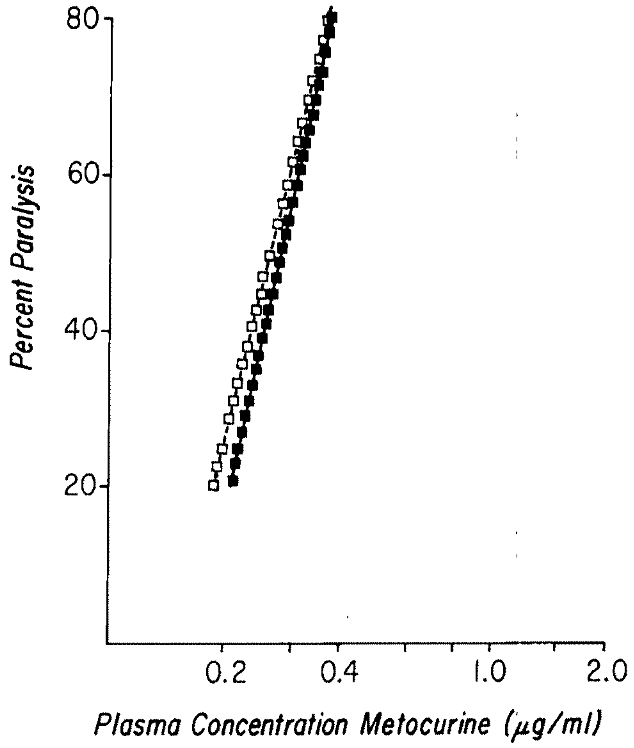

Figure 6. Regression lines for elderly (■——■) and younger controls (□—□) given metocurine 0.15 mg/kg, log plasma concentration–response between 20 and 80% paralysis; $n = 7$ for both groups.

younger patients. Because there is no change in concentration–response relationships between the elderly and the younger patients, our conclusion is that delayed elimination of *d*Tc and MTc in the elderly accounts for the prolonged effect of these drugs. This is the first report of the effects of age on the action, distribution, and elimination of dTc and MTc. The same principles derived from the present study also apply to pancuronium. McLeod et al. (5) attempted to correlate age with plasma clearance and volume of distribution in patients whose ages ranged from 20 to 86 yr. They found a correlation only with plasma clearance. Somogyi (15), in responding to McLeod, presented data showing no correlation between clearance and age after administration of pancuronium. The most recent and complete study of the kinetics and dynamics of pancuronium in the elderly is by Duvaldestin et al. (6). They found that in elderly patients (over 75 yr), the time for recovery of twitch tension was significantly prolonged. In addition, in the elderly, plasma clearance was decreased, elimination half-life prolonged, and urinary excretion of pancuronium decreased. The dose–response and plasma concentration–response relationships in the elderly were comparable to the control group. This evidence led them to conclude that pancuronium exerts a prolonged effect on the elderly, because of delayed elimination of the drug, and the pharmacodynamics of pancuronium are not altered by aging.

Stephens et al. (7) have recently reported on the pharmacokinetics of alcuronium in 2 groups of elderly patients. One group of patients had aortic aneurysm resection or total hip replacement with substantial blood loss, while the second group of elderly patients had minimal blood loss. The group of elderly patients with minimal blood loss exhibited a significantly prolonged elimination half-life and a significantly decreased plasma clearance. Although the authors did not measure duration of action of a dose of alcuronium on the basis of pharmacokinetics, it is very likely that the drug's action could be prolonged in elderly patients.

It appears that 3 long-acting muscle relaxants so far studied in the elderly, *d*-tubocurarine, metocurine, and pancuronium, have a prolonged effect as a result of delayed drug distribution and elimination. The fourth, alcuronium, exhibits kinetic changes that could lead to a prolonged duration of action.

Vecuronium and atracurium, both muscle relaxants of intermediate duration of action, have been

Table 3. Duration of Action of *d*-Tubocurarine (minute dose 0.3 mg/kg)

Recovery twitch height	Young controls $n = 7$, Mean ± SD (30–56 yr)	Elderly $n = 7$, Mean ± SD (70–87 yr)	*P*
25%	43 ± 12	64 ± 22	NS
50%	65 ± 14	114 ± 34	<0.02
75%	92 ± 21	158 ± 46	<0.02
Recovery index, 25–75%	48 ± 12	94 ± 32	<0.02

Table 4. Duration of Action of Metocurine (minute dose 0.15 mg/kg)

Recovery twitch height	Young controls $n = 7$, Mean ± SD (30–59 yr)	Elderly $n = 7$, Mean ± SD (73–83 yr)	*P*
25%	33 ± 14	63 ± 49	NS
50%	55 ± 14	118 ± 52	<0.05
75%	80 ± 19	173 ± 69	<0.02
Recovery index, 25–75%	47 ± 10	110 ± 35	<0.01

studied in the elderly. d'Hollander et al. (8) reported that the recovery index was prolonged in patients older than 60 yr who were receiving vecuronium. In a preliminary report, Rupp et al. (9) found elderly patients (70–84 yr) to have a significantly lower plasma clearance and volume of distribution than their controls. In determining pharmacodynamic parameters, they reported a steady-state concentration that results in 50% paralysis to be the same between the elderly and their controls. Unlike d'Hollander, they did not find any difference in the recovery index between the elderly and their controls. d'Hollander et al. (16) have studied atracurium in the elderly. They found that there was no significant difference between the dose required to produce a steady-state paralysis or the times required for recovery of twitch height in elderly patients, compared with younger groups of patients. The authors felt that the absence of age-related changes in dosage or recovery time was related to the mechanism of inactivation of atracurium: auto-decomposition by "Hoffman elimination" or by nonspecific plasma hydrolysis.

In summary, in this study we have found a prolonged effect of *d*Tc and MTc in the elderly, if the drugs are administered on a mg/kg basis. Delayed elimination appears to account for this effect. In addition, all of the studies of long-acting nondepolarizing muscle relaxants in the elderly have reported changes in kinetics that could cause prolonged effects of these drugs. In the case of vecuronium, a relaxant of intermediate action, there are conflicting reports as to the prolonged duration of action. The action of atracurium, which depends on "Hoffman elimination" or nonspecific plasma hydrolysis for elimination, rather than the kidney, does not appear to be affected by increasing age.

These findings are of considerable import. The elderly represent a large and increasing patient population. In our own clinic, the elderly (older than age 70) comprise 15% of those patients anesthetized for surgical procedures. The majority of these patients received muscle relaxants. Special care should be exercised in administering muscle relaxants to these patients. Downward adjustment of the dose given, together with careful monitoring of neuromuscular transmission should prevent overdose in the elderly patient.

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Dose-related Prolongation of the Bleeding Time by Intravenous Nitroglycerin

Peter R. Lichtenthal, MD, Ennio C. Rossi, MD, Gerlinde Louis,
Karen A. Rehnberg, BS, Leonard D. Wade, MS, Lawrence L. Michaelis, MD,
Ho-Leung Fung, PhD, and Paola Patrignani, ScD

LICHTENTHAL PR, ROSSI EC, LOUIS G, REHNBERG KA, WADE LD, MICHAELIS LL, FUNG HL, PATRIGNANI P. Dose-related prolongation of the bleeding time by intravenous nitroglycerin. Anesth Analg 1985;64:30–33.

The effects of intravenous nitroglycerin (NTG) upon the bleeding time, platelet aggregation response, and plasma 6-keto-PGF$_{1\alpha}$ concentration were measured in 17 patients about to undergo coronary bypass grafting. NTG produced a dose-related prolongation of the bleeding time that correlated with the accompanying decrease in systolic blood pressure. Platelet aggregation was not affected and measurements of 6-keto-PGF$_{1\alpha}$ failed to reveal detectable levels (< 10 pg/ml) either before or after NTG infusion. This suggests that the prolonged bleeding time associated with NTG infusion may be due to vasodilation and increased venous capacitance, rather than altered vascular–platelet interaction.

Key Words: PHARMACOLOGY—nitroglycerin. ANESTHETIC TECHNIQUES, HYPOTENSIVE—nitroglycerine. BLOOD—coagulation.

Nitroglycerin (NTG) in clinically effective concentrations stimulates prostacyclin (PGI$_2$) synthesis by endothelial cells (1) and bovine coronary arteries (2). Because PGI$_2$ is a potent inhibitor of platelet function (3–5), these observations suggest a mechanism by which NTG could act as an inhibitor of platelet function in vivo. In a preliminary communication we demonstrated that NTG prolonged the bleeding time in human subjects (6), an observation recently confirmed by Ring et al. (7). We have expanded these initial studies and now report the effects of intravenous NTG upon measurements of bleeding time, platelet aggregation response, and the PGI$_2$ hydrolysis product (6-keto-PGF$_{1\alpha}$) in 17 patients.

Methods

Sixteen men and three women (aged 36–73 yr) scheduled for coronary bypass grafting were the subjects of this study. After we obtained informed consent, patients received intravenous NTG for the purpose of blood pressure control. No patients were medicated with NTG ointment or patches on the day of surgery.

In the operating room, routine intravenous and monitoring lines including electrocardiogram, an arterial line, and a flow-directed pulmonary artery catheter were put in place. No peripheral intravenous lines were placed on the right side of any of the study patients, so that fluid administration would not influence the results of template bleeding time tests, which were always performed on the patient's right inner forearm. After this was completed a template bleeding time (8) was performed, and blood was obtained by venipuncture for platelet aggregation studies, plasma NTG concentrations, and assay of 6-keto-PGF$_{1\alpha}$. An NTG infusion (30 mg in 250 ml of 5% dextrose in water, American Critical Care, McGaw Park, IL) was begun at 60 μg/min and modified to maintain systolic blood pressure between 90–120 mm Hg. When systolic blood pressure had declined to between 110–120 mm Hg, the rate of NTG infusion was decreased and a second bleeding time was measured. A second blood sample was then obtained for aggregation studies, plasma NTG level, and 6-keto-PGF$_{1\alpha}$ assay. After the second set of blood samples was obtained, anesthesia was administered and surgery was begun.

Bleeding times were measured by Simplate II (Gen-

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Address correspondence to Dr. Lichtenthal, Department of Anesthesia, Northwestern University School of Medicine, 303 E. Chicago Avenue, Chicago, IL 60611.

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eral Diagnostics) (8). Platelet aggregation studies were performed in a platelet aggregometer according to the method of Born (9). Platelet rich plasma (PRP) was prepared by differential centrifugation of blood mixed in 3.8 g/100 sodium citrate in a 9:1 ratio. Before NTG infusion and after blood pressure was brought under control, platelet counts in PRP were 302,000 ± 128,000 and 297,000 ± 108,000, respectively. Platelet responses to ADP (1.25, 1.5, 2.5, and 5 μM), epinephrine (8 μM), arachidonic acid (2 mM), and several concentrations of collagen were measured. The aggregation response to collagen was expressed as K_d (the collagen concentration required to produce one-half maximum aggregation velocity). The greater the K_d (i.e., collagen requirement), the less responsive the platelets (10). Although none of the patients received aspirin or other known cyclooxygenase inhibitors, two patients demonstrated markedly abnormal baseline aggregation studies [i.e., impaired aggregation with arachidonic acid, absence of secondary aggregation with ADP (5 μM) and epinephrine (8 μM), and markedly elevated collagen K_d values (> 4.0 μg/ml; normal, 0.4–2.0 μg/ml)], and were eliminated from the study. In an additional patient, platelet studies could not be performed for technical reasons. Although propranolol may alter platelet function (11), eight patients who received propranolol preoperatively had normal baseline aggregation and were retained in the study.

The NTG plasma concentration was measured according to the method of Yap et al. (12). The NTG detection limit was 0.2 ng/ml, and the coefficient of variation was 10% at concentrations below 1.0 ng/ml, and < 10% at concentrations above 1.0 ng/ml. Assays for 6-keto-PGF$_{1\alpha}$ were performed according to the method of Patrono et al. (13). Statistical analysis was by Student's *t*-test and correlation coefficients (*r*) were calculated according to the method of least squares.

Results

The amount of NTG infused varied between 7–230 μg/kg and produced decreases in systolic blood pressure that ranged from 14 to 90 mm Hg. When the log of the NTG dose was plotted against the observed decline in systolic blood pressure, a positive correlation was obtained ($r = 0.65$; $P < 0.005$).

The platelet count was unchanged after NTG infusion (preinfusion, 169,000 ± 49,000; after blood pressure was controlled, 173,000 ± 56,000). However, the bleeding time was prolonged from 6.1 ± 1.7 min to 8.1 ± 2.5 min (difference in paired samples 2.0 ± 0.4; $P < 0.001$) (Fig. 1). NTG had no effect upon platelet aggregation. The minimum concentration of ADP required to induce secondary wave platelet aggregation was increased in four patients after infusion, unchanged in nine, and decreased in three. Similarly, the aggregation response to epinephrine and arachidonic acid was unchanged, and the collagen K_d, which was 0.9 ± 0.7 μg/ml collagen before infusion, remained stable at 1.0 ± 0.7 μg/ml collagen after blood pressure was brought under control (Fig. 1). Review of the initial nine cases revealed that the change in bleeding time correlated with the total NTG dose ($r = 0.75$; $P < 0.02$), but not with the NTG plasma concentration ($r = 0.45$; *P*, not significant). For this reason, measurements of plasma NTG concentrations, which ranged between 0.2 and 54 ng/ml, were discontinued. Analysis of all 17 patients confirmed the positive correlation between the log of the total NTG dose and the change in bleeding time ($r = 0.77$, $P < 0.001$) (Fig. 2). Moreover, when the decline in systolic blood pressure was plotted against the prolongation in bleeding time, a statistically significant positive correlation was also obtained ($r = 0.53$, $P < 0.05$). Measurements of 6-keto-PGF$_{1\alpha}$ failed to reveal detectable levels (< 10 pg/ml) in any of the patients either before infusion or after blood pressure was brought under control.

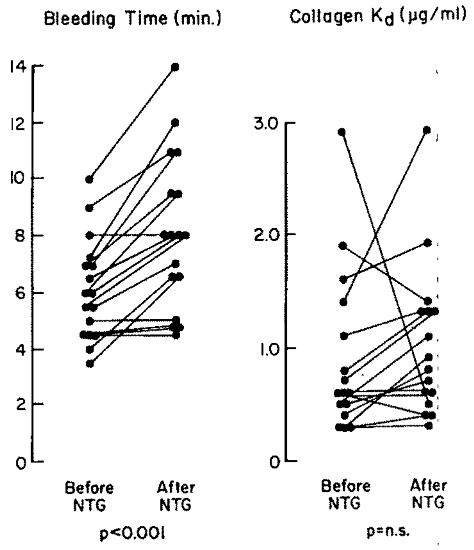

Figure 1. Bleeding times and platelet responsiveness to collagen (K_d) before and after nitroglycerin (NTG) infusion. Note that bleeding time is prolonged after NTG infusion ($P < 0.001$), while collagen K_d is unchanged.

Discussion

Intravenous nitroglycerin produces a dose-related prolongation of the bleeding time that is proportional to the accompanying decrease in systolic blood pressure. The lack of a demonstrable correlation between change in bleeding time and plasma NTG concentra-

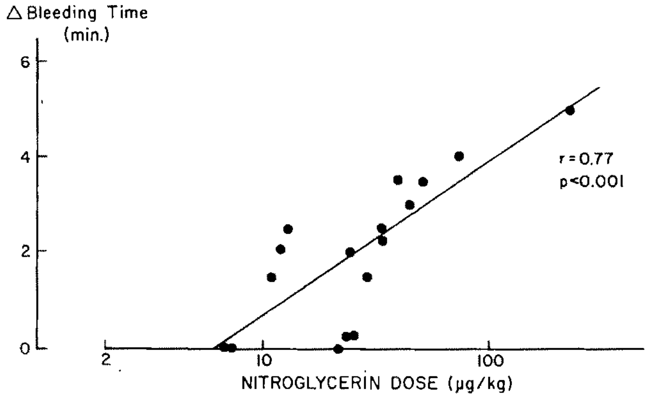

Figure 2. Correlation between change in bleeding time and NTG dose.

tion may be explained partially by the unusual pharmacokinetic features of NTG (14). For example, McNiff et al. (15) estimated that only about 1% of the total body load of NTG is found in plasma. Thus plasma NTG concentration may be greatly altered by minor fluctuations in the degree of drug binding to the large tissue pool, and as such, may serve as a variable index of its pharmacologic action (14).

Although a preliminary communication described inhibition of platelet aggregation (6), more complete studies reported here fail to uphold the inhibitory effect of NTG upon platelet aggregation and are consistent with the reports of others (7,16) who were similarly unable to detect an effect of NTG upon ex-vivo platelet aggregation. The lack of a demonstrable platelet defect after NTG infusion is consistent with both the low concentration of 6-keto-$PGF_{1\alpha}$ (< 10 pg/ml) observed and a concentration of PGI_2 below the threshold required to inhibit ADP-induced platelet aggregation in vitro (~ 34 pg/ml) (17). However, the inability to demonstrate impaired platelet function does not eliminate PIG_2 as the mediator of NTG-induced prolongation of the bleeding time.

Although recent evidence indicates that PGI_2 is not a circulating hormone, PIG_2 may, nonetheless, play an important role in localized platelet–vascular interactions (18). FitzGerald et al. (19) and Blair et al. (20) have shown that the upper limit of the baseline plasma 6-keto-$PGF_{1\alpha}$ concentration in humans ranges between 2.5 and 3.0 pg/ml. Because the methods employed in this study had a detection limit of 10 pg/ml, we cannot rule out a possible 3–4-fold increase of PGI_2 production after NTG infusion. Such an increase might conceivably affect local platelet–vascular interactions without inducing a demonstrable defect in platelet aggregation.

Recently Ring et al. (7) demonstrated that NTG-induced prolongation of the bleeding time is abolished by aspirin given 2–3.5 hr before NTG administration, but reemerges 48 hr after aspirin ingestion. The 48-hr recovery time of this NTG effect is roughly equivalent to the time required for recovery of vascular cyclooxygenase in endothelial cell cultures exposed to aspirin (21). This suggests that the effect of NTG upon the bleeding time may indeed be mediated by PGI_2. On the other hand, Fitzgerald et al. (22) did not detect an increase in urinary prostacyclin metabolites after NTG infusion. Although this latter observation would seem to eliminate circulating PGI_2 as the mediator of the NTG effect, it does not rule out increased PGI_2 at the endothelial cell level influencing localized platelet–vascular interactions (18). Thus a role for PGI_2 as a mediator of NTG effects remains an open question.

Vascular factors may provide an alternative explanation for the effect of NTG upon the bleeding time. Recently Leier et al. (23) measured limb blood flow by venous occlusive plethysmography in patients receiving intravenous NTG. They demonstrated that intravenous NTG decreased limb vascular resistance and increased mean limb blood flow by approximately 20%. Although the bleeding time may be considered a measure of the platelet aggregation in vivo (24), vascular factors may also be involved. A prolonged bleeding time associated with vasodilation and increased limb flow "would be compatible with the idea that larger aggregates would be required to plug a dilated vessel" (24). Thus the prolongation in bleeding time induced by NTG may be due to vasodilation and increased venous capacitance, rather than altered local vascular–platelet interaction.

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Sodium Citrate Pretreatment in Elective Cesarean Section Patients

David M. Dewan, MD, Herbert M. Floyd, MD, John M. Thistlewood, MBBS, BSc, Terrence D. Bogard, MD, and Fred J. Spielman, MD

DEWAN DM, FLOYD HM, THISTLEWOOD JM, BOGARD TD, SPIELMAN FJ. Sodium citrate pretreatment in elective cesarean section patients. Anesth Analg 1985;64:34–7.

Thirty-two healthy term parturients undergoing elective cesarean section randomly received either no antacid (n = 10), 30 ml of 0.3 molar sodium citrate less than 60 min preoperatively (n = 11), or 30 ml of 0.3 molar sodium citrate longer than 60 min preoperatively (n = 11). Immediately after delivery, the stomach was emptied as completely as possible through a #18 Salem Sump tube passed orally. Mean gastric pH in the three groups was 1.8 ± 2.7 (SD), 5.0 ± 1.5, and 2.7 ± 1.2, respectively. Gastric pH was significantly higher in the short interval group than in either the control group or in patients receiving their sodium citrate more than 60 min in advance. Gastric volumes were similar. All control patients had a gastric pH less than 2.5. Nine percent of patients receiving sodium citrate less than 60 min in advance and 50% of patients receiving their sodium citrate longer than 60 min in advance had a pH of less than 2.5. Volumes exceeding 25 ml occurred with equal frequency. No patient in the short interval group had a combination of both pH of less than 2.5 and a volume exceeding 25 ml. This combination occurred with equal frequency in control patients (64%) and in those patients receiving their sodium citrate more than 60 min in advance (50%). We conclude that sodium citrate effectively increases gastric pH when given less than 60 min prior to the induction of anesthesia.

Key Words: GASTROINTESTINAL TRACT—antacids. COMPLICATIONS—aspiration. ANESTHESIA—obstetric.

Aspiration of gastric contents persists as a leading cause of maternal mortality (1,2). Laboratory research suggests greater morbidity and mortality when the volume of aspirate exceeds 0.4 ml/kg and the pH is less than 2.5 (3,4). Most attempts to decrease the threat of aspiration focus on increasing gastric pH, because gastric volume proves difficult to alter reliably. Antacids effectively increase gastric pH (3,5). Unfortunately, their widespread use has not eliminated material mortality (1). Pulmonary injury caused by emulsified antacids aspirated into the lungs may explain the failure of some types of antacid prophylaxis (6). Clear solutions, buffered to the same pH as emulsified antacids, on the other hand, do not damage lungs if aspirated (6).

Sodium citrate, an excellent in vitro buffer of gastric pH, is a clear solution, does not injure the lungs if aspirated, and offers an alternative to emulsified antacids (7). Its effectiveness in clinical practice remains, however, uncertain. In a previous study, for example, we administered 30 ml of a 0.15 molar solution of sodium citrate in a series of parturients and found that 85% had a gastric pH of less than 2.5 at the time of sampling (8). We hypothesized that sodium citrate might have a short duration of action, because the mean interval between drug administration and sampling (80 min) was significantly longer than intervals noted in earlier studies that demonstrated sodium citrate to be more effective in increasing gastric pH above 2.5 (7,9). In the present study we examined this possibility in a series of parturients in whom we controlled the sampling interval.

Methods

The Clinical Research Practices Committee approved the protocol, and 32 healthy term parturients scheduled for elective cesarean section under general anesthesia participated in the study after giving informed consent. We randomly assigned parturients to one of three antacid pretreatment regimens: no antacid; 30 ml 0.3 molar sodium citrate (sodium citrate solution: 88.2 g sodium citrate dissolved in 1000 ml distilled water; pH 8.4) given orally less than 60 min preop-

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Address correspondence to Dr. Dewan, Section of Obstetric Anesthesia, Forsyth Memorial Hospital, 3333 Silas Creek Parkway, Winston-Salem, NC 27103.

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Table 1. Gastric Sampling in Untreated Control Patients and Patients Receiving Sodium Citrate

	Control (n = 11)	Short interval[a] (n = 11)	Long interval[b] (n = 10)
Age (yr)	23.2 ± 3.4	25.7 ± 3.8	21.0 ± 3.7
Height (cm)	163.6 ± 7.9	164.1 ± 8.1	162.8 ± 5.3
Weight (kg)	77.6 ± 17.5	85.7 ± 17.0	79.3 ± 14.9
Interval (min)	—	37.4 ± 10.2	76.3 ± 22.6

Values given as mean ± SD.

[a] Short interval, antacid sodium citrate administered less than 60 min preoperatively.

[b] Long interval, sodium citrate given more than 60 min preoperatively.

Table 2. Mean Gastric Volumes and pH Levels in Control Patients and in Patients Receiving Sodium Citrate Pretreatment

	Control (n = 11)	Short interval (n = 11)	Long interval (n = 10)
Volume (ml)	32.2 ± 21.9	46.6 ± 26.8	34.3 ± 14.0
pH (mean)	1.8 ± 0.3	5.0 ± 1.5[a]	2.7 ± 1.2

[a] $P < 0.05$ when compared to control and long interval groups.
Values are mean ± SD.

eratively; and 30 ml 0.3 molar sodium citrate given more than 60 min preoperatively. The hospital pharmacy prepared the sodium citrate solution, which was then stored in a refrigerator until immediately before use. We induced anesthesia rapidly with 4.0 mg/kg of thiopental intravenously, and intubated the trachea after an intravenous bolus of 1.2 mg/kg of succinylcholine while applying cricoid pressure. After the intubation, we administered 66% nitrous oxide with 33% oxygen while maintaining muscle relaxation with an infusion of 0.1% succinylcholine. As soon as possible after intubation, we passed a #18 Salem Sump tube orally and aspirated the gastric contents as completely as possible to measure the volume and pH (Fischer accument pH meter, Model 1212) of each specimen. We compared the parturient groups for age, height, weight, interval between antacid premedication and sampling, and gastric pH and volume. Data were analyzed using the multivariant analysis of variance, t-test, and χ^2-test. We considered a P value of equal to or less than 0.05 as statistically significant.

Results

The groups were similar in age, height, and weight (Table 1). The mean sampling interval was 37.4 ± 10.2 min in the short interval group and 76.3 ± 22.6 min in the long interval group (Table 1). Volumes of gastric contents did not differ among the groups (Table 2). The short interval group had a mean gastric pH significantly higher than mean gastric pH levels in both the long interval and control groups. There was no statistical difference between the mean pH in the control group and the mean pH in patients who received their sodium citrate more than 60 min prior to sampling (Table 2).

Gastric pH was below 2.5 in all parturients who did not receive sodium citrate preoperatively (Table 3). Although there was no statistical difference in mean pH between the gastric specimens of the control group and those who received sodium citrate more than 60 min in advance, only 50% of patients in the long interval group had a gastric pH less than 2.5. This was significantly less than in the control group (Table 3). Only 9%, 1 of 11 patients, had a pH below 2.5 when sodium citrate was administered less than 60 min in advance, statistically better than pH values less than 2.5 in either of the other groups.

Gastric volumes greater than 25 ml occurred with similar frequency in all groups. Despite the apparently larger volume in the short interval group, regression analysis failed to demonstrate any relationship between gastric volume and sampling interval. Control patients were most likely to have both a low pH and a volume exceeding 25 ml (Table 3). Unlike the control or long interval groups, no patient had this potentially lethal combination when sodium citrate was given less than 60 min in advance. The administration of sodium citrate more than 60 min in advance offered no protection, when compared to the control patients.

Discussion

In 1973, Lahiri et al. found that 15 ml of 0.3 molar sodium citrate elevated gastric pH above 3.0 in 21 of 22 parturients (7). Later, however, Hester and Heath, using the same volume and concentration of sodium citrate, found no differences between treated and untreated control patients (10). They attributed the success of Lahiri et al. to faulty experimental design. Subsequent investigators doubled the volume of sodium citrate given, and thus the buffering capacity of antacid administered, and successfully increased the gastric pH (11). In our earlier study, 30 ml of a 0.15 molar solution had a buffering capacity equivalent to that used in Lahiri's (7) study using 15 ml of 0.3 molar sodium citrate, and 85% of our parturients had a gastric pH less than 2.5 (8). A short duration of action could explain the difference between our results and those of Lahiri et al. Our present results surprised us by confirming this explanation, both because Viegas and Wrobel successfully used a 15 ml volume of a 0.3

Table 3. Incidence of Gastric pH < 2.5 and Volumes > 25 ml in Controls and in Patients Receiving Sodium Citrate[a]

	Control (n = 11)	Short interval (n = 11)	Long interval (n = 10)
pH < 2.5	100% (11/11)[b]	9% (1/11)[b]	50% (5/10)[b]
Volume > 25 ml	64% (7/11)	91% (10/11)	80% (8/11)
pH < 2.5 and volume > 25 ml	64% (7/11)[c]	0% (0/11)[b]	50% (5/10)[c]

[a] Incidence is reported as a percentage of patients and as the number of affected patients per group.

[b] $P < 0.05$ when compared to other groups.

[c] $P < 0.05$ when compared to short interval group.

molar solution of sodium citrate (9,12) and because Gibbs et al. (13) did not find a relationship between gastric pH and the interval between antacid administration and sampling if the interval was less than 185 min. Recently, O'Sullivan and Bullingham observed that gastric emptying represents an important factor in determining the duration of action of antacids (14). When gastric emptying occurs swiftly, the antacid rapidly leaves the stomach and has a short duration of action. Factors that slow gastric emptying extended the duration of effect of antacids. Our patients received neither narcotics nor anticholinergics that might slow gastric emptying. Pocketing or layering of orally administered solutions within the stomach can also occur, and not only prevent adequate mixing of antacids with the gastric contents, but also delay gastric emptying (15). After antacid administration, our patients were never fully supine or in the head-up position, making pocketing or layering of sodium citrate within the stomach less likely. Rapid gastric emptying may also possibly explain the short duration of action we observed. Despite the fact that regression analysis failed to detect a statistical relationship between pH and interval between administration of sodium citrate and sampling of gastric content (Fig. 1), the elevated mean pH in the short interval group and the increased incidence of low pH in the long interval group suggest, when compared to the short interval group, a short duration of sodium citrate action. This becomes more apparent when examining parturients with both a low pH and gastric volumes above 25 ml, for we were unable to distinguish statistically between control patients and those patients in whom the time from administration to sampling was longer than 60 min. The trend of smaller gastric volumes in the long interval group, although not statistically significant, may reflect the passage of antacid from the stomach, and explain the low pH.

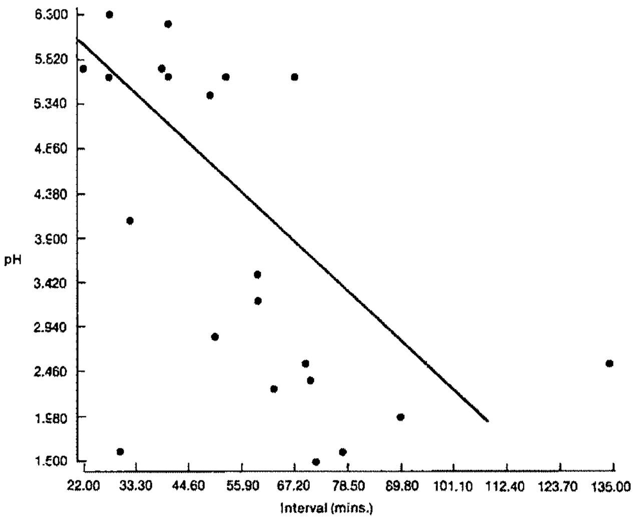

Figure 1. Regression analysis plotting pH versus intervals (min) for patients receiving 30 ml 0.3 molar sodium citrate preoperatively. Statistical analysis revealed no relationship between the two variables.

We were initially concerned that administering 30 ml of sodium citrate close to the time of induction of anesthesia might increase gastric volume. Because outcome from aspiration depends on both gastric volume and pH, larger gastric volumes might mitigate the beneficial effects of increased pH. The gastric volume in the short interval group was, however, not significantly greater than in either the control or the long interval groups. We recognize that simple aspiration of gastric contents is not a completely reliable method of measuring gastric volume. Dye dilution techniques are more accurate. Nevertheless, the gastric volumes in all three groups indicate some increased risk and, if anything, underestimate gastric volumes. The gastric volumes in our patients ranged from a low of 15 ml to a maximum of 100 ml, emphasizing that parturients have unpredictable gastric volumes. No parturient has an "empty" stomach.

We conclude that sodium citrate represents an effective antacid for elective cesarean section patients only when given less than 60 min preoperatively. It may prove ineffective when administered more than 60 min preoperatively. No techique, including sodium citrate administration, completely eliminates the threat of aspiration. Suspicion that all parturients may have a full stomach, liberal use of regional anesthesia, meticulous attention to details, and, when general anesthesia becomes necessary, securing the airway in the safest fashion, all form necessary aspects of any anesthetic plan for women delivering by cesarean section.

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Computer-controlled Regulation of Sodium Nitroprusside Infusion

Lewis J. Meline, Dwayne R. Westenskow, PhD, Nathan L. Pace, MD, and Mark N. Bodily, BS

MELINE LJ, WESTENSKOW DR, PACE NL, BODILY MN. Computer-controlled regulation of sodium nitroprusside infusion. Anesth Analg 1985;64:38–42.

We built and tested a combined proportional/derivative and minimum variance adaptive control algorithm for the regulation of blood pressure using sodium nitroprusside (SNP). In ten dogs the pressure was reduced by 30 mm Hg for 1 hr. The blood pressure came to within 5 mm Hg of the desired pressure in 1.7 ± 4 min and after 3.4 ± 0.3 min it remained within ± 5 mm Hg of the desired value. During the nitroprusside infusion, bolus doses of epinephrine and SNP as well as phlebotomy were used to challenge the controller. The controller responded rapidly and effectively so that blood pressure remained stable throughout each challenge. Control was achieved in ten dogs with very different sensitivities to SNP. After 1 hr of SNP infusion, the rate of SNP infusion required to maintain a 30 mm Hg reduction in pressure averaged 112 ml/hr with a standard deviation of 108 ml/hr. Adaptive control met the challenge of large differences in sensitivity and maintained the desired blood pressure.

Key Words: ANESTHETIC TECHNIQUES—hypotensive. BLOOD PRESSURE—hypotension. COMPUTER PROGRAMS.

Sodium nitroprusside (SNP) is a rapidly acting vasodilator that relaxes the smooth muscle of the peripheral arterial and venous vasculature. Indications for use of SNP include management of hypertensive crisis, of myocardial dysfunction, and of myocardial ischemia, as well as the induction of controlled hypotension (1–3). Meticulous care and close attention are required during drug infusion because of the rapid onset and the high degree of variability in response among patients. Computer rather than manual control of the infusion of SNP may improve safety and provide better control of the blood pressure.

Several algorithms have been used to automatically control the infusion of SNP. Proportional, integral, and differential (PID) and "wait and see" controllers do not adapt to the varying sensitivities among patients and have to be readjusted for a very sensitive or insensitive patient (4–9). Approaches using adaptive algorithms (minimum variance, model reference, and adaptive PID) have the disadvantage of requiring a 10–15 min learning period before control can be initiated (10–15). During this learning time, the controller computes the patient's sensitivity to SNP and automatically adjusts its gain accordingly. During anesthesia it is desirable to lower blood pressure quickly, without waiting for a learning period. In an animal study we tested a combined proportional and derivative (PD) and minimum variance adaptive control algorithm without a learning period.

Methods

Control Algorithm

Our system used a self-tuning controller based on the minimum-output-variance theory of Clarke (16). An animal's response to SNP is described by the following:

$$y(t) = f_0 y(t - 1) + \cdots + f_n y(t - n) + g_0 u(t - k) + \cdots + g_n u(t - k - n) + \text{error}, \quad (1)$$

where $y(t)$ equals blood pressure; $y(t - 1)$, previous blood pressure; $u(t - k)$, SNP infusion rate; $u(t - k - 1)$, previous SNP rate; error, uncorrelated noise; k, input delay time; $f_0, \cdots, f_n, g_0, \cdots, g_n$, coefficients for the animal; and t, integer time index.

Equation (1) predicts the current blood pressure ($y(t)$) given the present and previous SNP rates and previous blood pressures. If noise in the blood pressure measurement and irregularities in the SNP–pressure relationship are assumed to be zero for the purposes of this study (error = 0) and if the sample time is selected such that the transport time between drug delivery and drug effect can be ignored (t = 15 sec and k = 0), the rate of SNP administration that

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Address correspondence to Lewis J. Meline, University of Utah Medical Center, Salt Lake City, Utah 84132.

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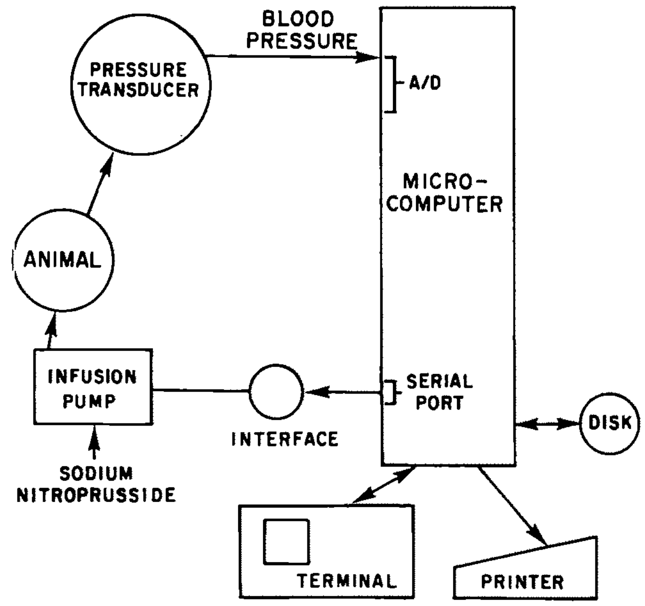

Figure 1. Block diagram of the computer controller for SNP infusion.

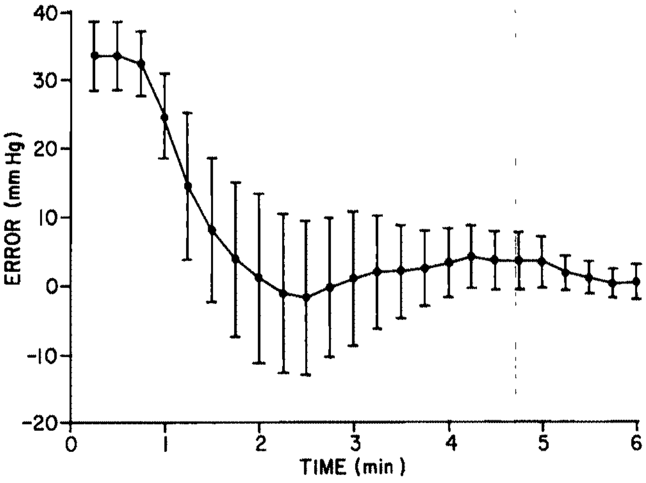

Figure 2. Average difference between the desired mean arterial blood pressure and the measured pressure (error) after initiating computer control. Each bar gives one standard deviation.

will produce a blood pressure of zero is the following:

$$u(t) = -[f_0y(t-1) + \cdots + f_ny(t-n) + g_1u(t-1) + \cdots + g_nu(t-n)]/g_0. \quad (2)$$

The infusion rate that will produce a nonzero pressure (y_d) is given by substituting $y_d - y(t)$ for $y(t)$. A recursive least squares technique is used to calculate the five f_i and g_i coefficients for each animal (16). Proportional and differential (PD) control terms are added in parallel with the minimum-variance algorithm. The PD terms are

$$u_p(t) = K_p\,[y_d - y\,(t)] \quad (3)$$

$$u_d(t) = K_d\,[y(t-1) - y(t)] \quad (4)$$

where K_p is [(weight (kg) − 10)/10] + 2, and $k_d = k_p/2$. The final SNP infusion rate becomes $u(t) + u_p(t) + u_d(t)$.

Equipment

The control algorithm was implemented using a Motorola EXORcisor II 6809-based microprocessor development system (Fig. 1). The SNP infusion rate was controlled via a serial data port to an IVAC 630 volumetric infusion pump with a computer interface module. Blood pressure from an intraarterial catheter and pressure monitor (Textronix 414) was interfaced through a 12-bit analog-to-digital converter. The SNP infusion rate and blood pressure were sampled every 15 sec and displayed in a video terminal (Perkin-Elmer 550) and stored on diskette (Motorola EXORdisc II). Control parameters and error signals were printed after every fifth sample period (Centronics 781).

Animal Preparation

Ten mongrel dogs (18–25 kg) were anesthetized with intravenous sodium thiopental (15–20 mg/kg) and their tracheas intubated. Anesthesia was maintained with 1.0% halothane, 50% nitrous oxide, and the balance oxygen. The inspired concentrations of halothane and nitrous oxide were adjusted to maintain the mean blood pressure at 110 ± 10 mm Hg before the SNP infusion was started. Mechnical ventilation was adjusted to maintain Pa_{CO_2} at approximately 35 mm Hg. Body temperature was kept at 37 ± 1°C using a heating pad. Normal saline (125 ml/hr) and drugs were administered through a forepaw vein. Percutaneous catheters were introduced into both femoral arteries, one for blood pressure determination and the other for rapid phlebotomy. A catheter was placed in a jugular vein for infusion of SNP (100 μg/ml). A pulmonary arterial catheter was placed via the other jugular vein for measurement of body temperature and cardiac output.

Once the preparation was complete, the controller was started and instructed to reduce the mean pressure by 30 mm Hg. This hypotension was maintained for 1 hr to test the long-term stability of the controller. Then the SNP infusion was stopped, allowing the blood pressure to increase. The controller was started a second time. When blood pressure was again stable 30 mm Hg below control pressure, a bolus of epi-

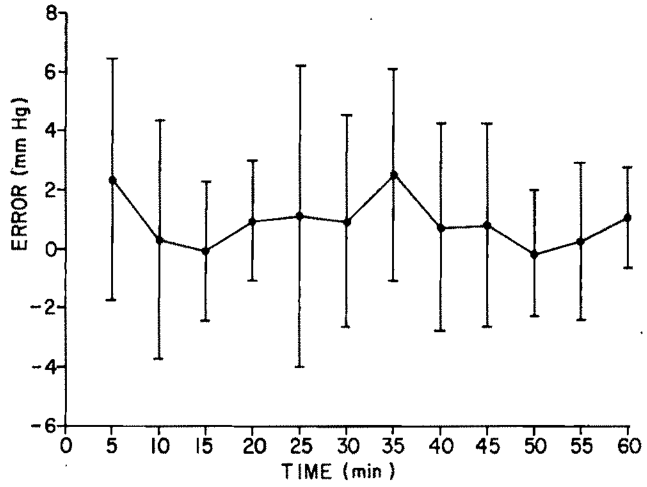

Figure 3. Error as measured in 10 dogs during 1 hr of computer-controlled hypotension (mean ± SD).

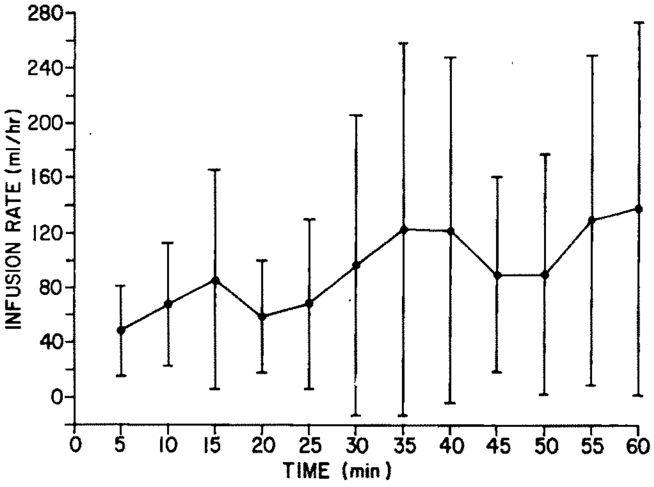

Figure 4. SNP infusion rate providing the result in Fig. 3 (mean ± SD).

nephrine (1 μg/kg) was given. Fifteen minutes later, a bolus of SNP was given; the bolus equaled the SNP infused during the previous 5 min. After 15 min, the continuous SNP infusion was stopped again and blood pressure again returned to control levels. The controller was started a third time. When pressure was stable, 500 ml of blood was removed over a 15 min period.

Means and standard deviations were calculated for all sample values. Other statistical methods included paired *t*-tests and Hotelling TSQUARE analysis. Alpha was set at 0.05.

Results

Figure 2 shows the average difference or error between the desired blood pressure and the measured blood pressure for all dogs during the third "on" response. The other two responses were similar. Averaging all "on" responses, the blood pressure came to within 5 mm Hg of the desired pressure in 1.7 ± 0.4 min (mean ± SD). The pressure then continued to decrease reaching a level 8.9 ± 10.5 mm Hg below the desired value. By 3.4 ± 0.3 min after starting, pressures remained within ± 5 mm Hg of the desired value.

During the hour of hypotension (Fig. 3), no significant variation of the actual pressure from the desired pressure occurred (Hotelling TSQUARE). Over this period the SNP infusion rate increased from 48 ± 10 to 112 ± 108 ml/hr (Fig. 4).

Figure 5 shows the response to the bolus of epinephrine. The pressure increased an average of 44.3 ± 19.28 mm Hg above and then decreased 10.3 ± 6.5 mm Hg below the desired pressure. The controller returned the pressure to within 5 mm Hg of the desired pressure in 4.3 ± 2.6 min.

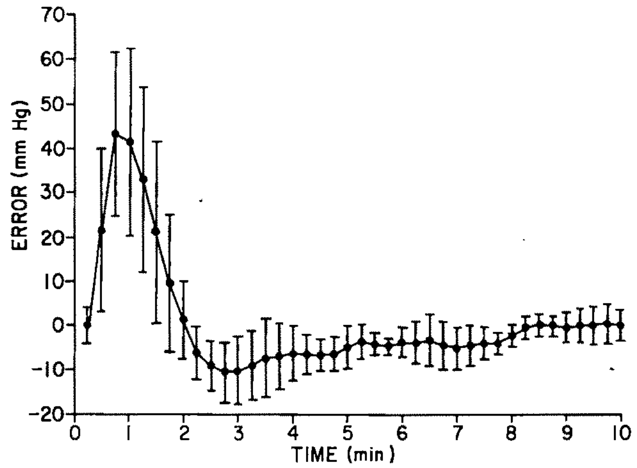

Figure 5. Error caused by epinephrine bolus (mean ± SD).

In response to the SNP bolus (Fig. 6), the controller stopped the infusion of nitroprusside almost immediately. The pressure decreased an average of 27.5 ± 6.1 mm Hg below then increased 14.1 ± 6.3 mm Hg above the desired pressure. A mean of 5.5 ± 2.1 min was required for the controller to return the pressure to within ± 5 mm Hg of the desired pressure.

During bleeding the pressure remained within 5 mm Hg of the desired pressure (Fig. 7) while the infusion rate fell from a mean 92 ml/hr to a mean of 20 ml/hr (Fig. 8). The controller maintained stability throughout each challenge.

Discussion

Ideally one would like a system to produce hypotension in 2–3 min and to keep mean arterial blood pres-

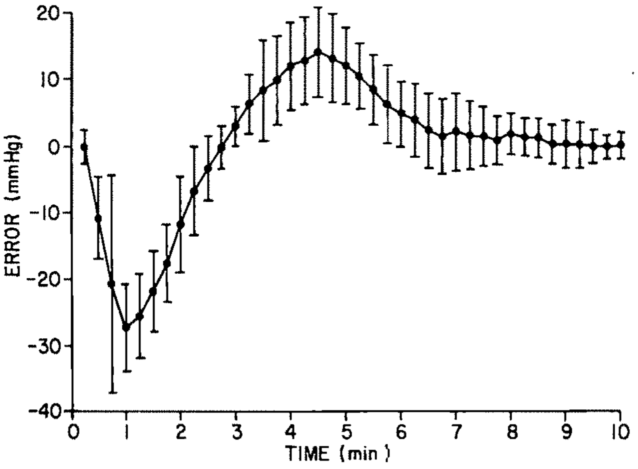

Figure 6. Error caused by SNP bolus (mean ± SD).

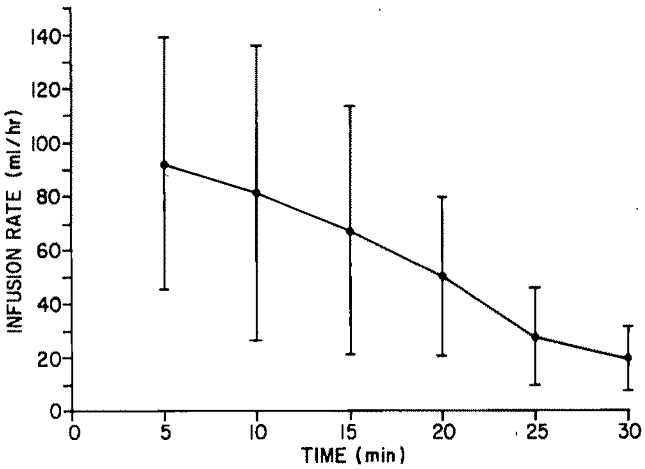

Figure 8. SNP infusion during bleeding (mean ± SD).

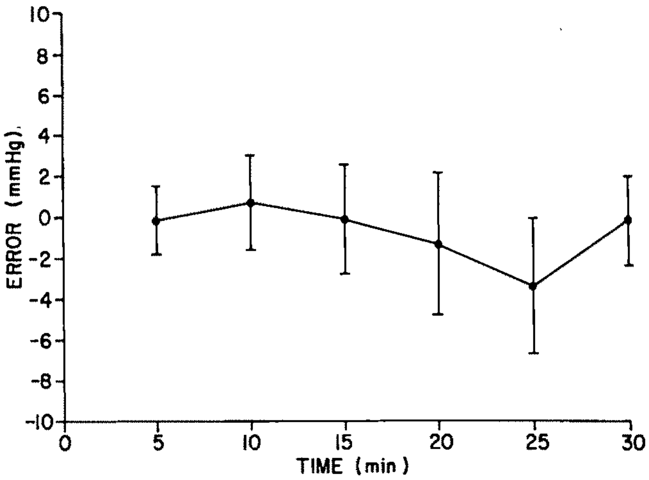

Figure 7. Error during bleeding 500 ml of blood was removed during the first 15 min (mean = SD).

sure within 5 mm Hg of the desired pressure thereafter. Control should be achieved regardless of the patient's sensitivity to SNP. Control should also be maintained during sympathetic stimulation or hypovolemia. Our study protocol was designed to evaluate an adaptive controller, to measure its transient response, to test its ability to compensate for varying drug sensitivity, and to test its ability to maintain stability during challenges.

Our controller reduced blood pressure and kept it within 5 mm Hg of the desired level after 3.4 ± 0.3 min. Other adaptive controllers have shown similar transient response, but have required a learning or adaptation period before control began (11,12,14). Our parallel combination of PD control and minimum variance control seems to provide a good solution: a controller that can control without first learning. The PD terms directed the blood pressure toward the desired level until the minimum variance controller calculated the specific control parameters for the animal. In steady state, the PD terms have little effect and the minimum variance algorithm provides control.

Control was achieved in ten dogs with very different sensitivities to SNP. After 1 hr of SNP infusion, the rate of SNP infusion required to maintain a 30 mm Hg reduction in pressure averaged 112 ml/hr with a standard deviation of 108 ml/hr. Adaptive control met the challenge of large differences in sensitivity and maintained the desired pressure.

Under clinical conditions a microprocessor SNP controller would eliminate the tedious task of manually maintaining blood pressure by frequently adjusting the SNP infusion rate. However, before our controller is ready for use in operating rooms or intensive care units, safeguards need to be included to ensure the integrity of the blood pressure signal. Though the control algorithm seems capable of handling differences in SNP sensitivity and catastrophic challenges in dogs, it needs a similar evaluation in humans.

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The Effects of Isoflurane and Isoflurane–Nitrous Oxide Anesthesia on Brainstem Auditory Evoked Potentials in Humans

Pirjo H. Manninen, MD, FRCP(C), Arthur M. Lam, MD, FRCP(C), and James F. Nicholas, MD

MANNINEN PH, LAM AM, NICHOLAS JF. The effects of isoflurane and isoflurane–nitrous oxide anesthesia on brainstem auditory evoked potentials in humans. Anesth Analg 1985;64:43–7.

Monitoring of brainstem auditory evoked potentials (BAEP) during neurological surgery can provide useful information. However, in order to interpret intraoperative BAEP changes, it is necessary to delineate the influence of anesthesia, including inhalation agents. In this study, we examined the influence of isoflurane and isoflurane–nitrous oxide anesthesia on BAEP in ten healthy volunteers during normothermic, normocapnic, and normotensive conditions. Isoflurane significantly increased the latencies of peaks III, IV, and V at all end-tidal concentrations studied (1.0%, 1.5%, and 2.0%). Addition of 50% nitrous oxide did not influence these findings. The increase in latencies with isoflurane anesthesia, however, was nonlinear and appeared to plateau after 1.5%. We suggest that during isoflurane anesthesia, an intraoperative increase in peak V latency beyond 1.0 msec is best explained by factors other than direct effects of isoflurane.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHETICS, GASES—nitrous oxide. BRAIN—evoked potentials.

During operative procedures in the posterior fossa it is desirable to be able to monitor brainstem function because manipulation and retraction of the brainstem may cause ischemia, infarction, or both. Brainstem auditory evoked potentials (BAEP) are the electrophysiological responses generated in the auditory pathway in the brainstem in response to acoustic stimulation. A characteristic wave form consisting of seven individual peaks can be identified, and the purported neurogenerators are peak I, the acoustic nerve; peak II, cochlear nucleus; peak III, the superior olive; peak IV, lateral lemniscus; peak V, inferior colliculus; peak VI, medial geniculate; and peak VII, thalamocortical radiations (1). A simpler interpretation is to consider peaks I and II as originating from the peripheral portion of the auditory nerve, peak III from the pons, peaks IV and V from the midbrain, and peaks VI and VII as cortical components. As a noninvasive method of monitoring the integrity of the auditory nerve pathway through the brainstem, continual recording of BAEP has been found to be useful as an intraoperative monitor during certain neurosurgical procedures (1–3). However, the importance of maintaining stable anesthetic conditions to allow accurate recording cannot be overemphasized, because different anesthetic agents may have different influences on BAEP in man. Enflurane increases the latencies of the different peaks (4), while halothane and barbiturates have no influence on BAEP in humans (5,6). The influence of isoflurane on BAEP has not been studied in normal subjects under controlled conditions. The purpose of this study was to investigate the influence of isoflurane and isoflurane–nitrous oxide anesthesia on BAEP in a dose-related manner.

Methods

The study was approved by the Health Sciences Standing Committee on Human Research of the University of Western Ontario. Informed consent was obtained from each subject. We studied ten young healthy subjects of ASA physical status I, mean age 28 yr, admitted for minor elective surgery. The study was conducted prior to any surgical manipulation in a quiet, comfortable environment.

BAEP were recorded in a standardized manner in all subjects using a Nicolet CA 1000 averager. The evoked potentials were recorded from the vertex (CZ) in reference to the ipsilateral ear lobe using the con-

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Address correspondence to Dr. Lam, Department of Anesthesia, University Hospital, PO Box 5339, Postal Station A, London, Ontario, Canada N6A 5A5.

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Table 1. BAEP Latencies (msec ± SD) with Isoflurane Alone

End-tidal isoflurane concentration	Peak latencies						
	I	II	III	IV	V	I–V	III–V
0% (awake) (n = 10)	2.10 ± 0.15	3.26 ± 0.11	4.27 ± 0.13	5.54 ± 0.16[a]	6.08 ± 0.18	3.99 ± 0.29	1.81 ± 0.15
1% (n = 8)	2.27 ± 0.14	3.37 ± 0.11[b]	4.55 ± 0.18[b]	6.07 ± 0.27[a,b]	6.68 ± 0.24[b]	4.41 ± 0.28[b]	2.13 ± 0.11[b]
1.5% (n = 9)	2.22 ± 0.20	3.41 ± 0.18[b]	4.59 ± 0.20[b]	6.25 ± 0.16[a,b]	6.78 ± 0.22[b]	4.56 ± 0.32[b]	2.20 ± 0.13[b]
2.0% (n = 8)	2.33 ± 0.21[b]	3.39 ± 0.18	4.59 ± 0.18[b]	6.11 ± 0.12[a,b]	6.78 ± 0.27[b]	4.55 ± 0.33[b]	2.19 ± 0.12[b]

[a] Number of subjects is $n - 1$ because one subject did not have peak IV.
[b] Significantly different from awake values, $P < 0.05$.

tralateral ear lobe as ground (A1 and A2 according to the International 10-20 electrode system). Silver/silver chloride electrodes were attached with collodion. Impedance was maintained at less than 3000 Ω. Disposable ear inserts were used to deliver the auditory stimulus (this causes a delay of 0.5 msec in latency of all peaks when compared to data obtained using ear insert transducers). The subject's threshold hearing level for each ear was determined prior to the study. Ipsilateral monaural alternating clicks at 60 dB above threshold, with contralateral masking of 30 dB below the stimulating intensity, were delivered at a rate of 21.1 Hz. Sensitivity was set at 10 μV and bandpass filter from 150–1500 Hz. At least 1000 sweeps of 10-msec duration were averaged.

BAEP were recorded in the following settings: awake control; end-tidal isoflurane concentration 1.0%; 1.5%; and 2.0%. To assess the influence of nitrous oxide, evoked potentials were also recorded with the addition of 50% nitrous oxide at the same isoflurane concentrations as listed. Because of the time constraint, we were unable to record BAEP at all anesthetic concentrations in every subject. However, a minimum of seven subjects was studied in each level of anesthesia. In addition, to eliminate the potential influence of time and minor temperature change, the order of the anesthetic end-tidal concentrations, with and without nitrous oxide, was randomized.

Anesthesia was induced with 5 $mg \cdot kg^{-1}$ sodium thiopental, and 1 $mg \cdot kg^{-1}$ succinylcholine was administered to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane and 100% oxygen or with isoflurane in 50% nitrous oxide and 50% oxygen as outlined above. End-tidal CO_2 level was maintained between 34–38 mm Hg using mechanical ventilation. ECG, blood pressure, and temperature were continuously monitored using a standard electrocardiographic monitor, automatic blood pressure cuff (Dinamap), and a nasopharyngeal probe, respectively. Temperature was maintained within 1°C of preoperative values using a thermal blanket and warm intravenous infusion. Blood pressure was maintained at no less than 75% of preanesthetic value with intravenous infusion of Ringer's lactate solution. End-tidal CO_2, nitrous oxide, and isoflurane concentrations were monitored continuously using a mass spectrometer (Perkin-Elmer 1100). Each anesthetic end-tidal concentration was maintained for at least 15 min prior to recording BAEP. Duplicate tracings were recorded and stored on a computer disk for subsequent analysis.

For analysis of data, latencies and amplitudes of the first five peaks as well as interpeak latencies of I–V and III–V were measured and used for comparison purposes. One-way analysis of variance was utilized to compare the anesthetic states to the awake control state and two-way analysis of variance for the influence of nitrous oxide. Where indicated, Dunnett's test was used to detect any difference from awake control. Multiple comparison procedures (Scheffe's test) were used for comparisons between different anesthetic states. A P value of less than 0.05 was considered statistically significant.

Results

BAEP were successfully recorded in a reproducible manner in all subjects, and there were no complications. Temperature did not increase in any subject, never decreased below 35°C, and in eight out of ten subjects studied, temperature during anesthesia was unchanged from or within 0.5°C of awake values. The latencies of the first five peaks and the interpeak latencies during isoflurane anesthesia are shown in Table 1. The influence of nitrous oxide is shown in Table 2. A typical tracing from one subject showing the influence of isoflurane anesthesia on the BAEP is shown in Figure 1. Isoflurane increased the latencies of peaks III, IV, and V significantly above awake control levels at all levels of anesthesia. The addition of nitrous oxide did not influence these findings.

Changes in BAEP were not affected by increasing the depth of anesthesia. The increase in latencies occurred at 1.0% end-tidal isoflurane and no further

Table 2. BAEP Latencies (msec ± SD) with Isoflurane plus 50% N_2O

End-tidal isoflurane concentration	Peak latencies						
	I	II	III	IV	V	I–V	III–V
0% (awake) ($n = 10$)	2.10 ± 0.15	3.26 ± 0.11	4.27 ± 0.13	5.54 ± 0.16[a]	6.08 ± 0.18	3.99 ± 0.29	1.81 ± 0.15
1.0% ($n = 9$)	2.19 ± 0.17	3.41 ± 0.16[b]	4.56 ± 0.18[b]	6.06 ± 0.29[a,b]	6.68 ± 0.27[b]	4.44 ± 0.33[b]	2.13 ± 0.16[b]
1.5% ($n = 8$)	2.20 ± 0.18	3.44 ± 0.12[b]	4.54 ± 0.16[b]	6.08 ± 0.36[a,b]	6.67 ± 0.23[b]	4.47 ± 0.34[b]	2.13 ± 0.16[b]
2.0% ($n = 7$)	2.13 ± 0.27	3.36 ± 0.12	4.52 ± 0.12[b]	6.10 ± 0.37[a,b]	6.74 ± 0.24[b]	4.61 ± 0.39[b]	2.22 ± 0.13[b]

[a] Number of subjects is $n - 1$ because one subject did not have peak IV.
[b] Significantly different from awake values, $P < 0.05$.

increase was noted after 1.5%. Similar changes were noted for the interpeak latencies. Again, the addition of 50% nitrous oxide did not influence these findings. No consistent change in amplitude was observed.

Discussion

Changes in BAEP have been shown to occur during posterior fossa surgery and may be of value in monitoring brainstem function and integrity of the eighth nerve during such neurological procedures (1–3). Many variables can influence the recording and interpretation of these evoked potentials. Hypothermia may result in prolongation of the latency and temperature must therefore be carefully controlled and maintained during anesthesia (7). Latency also increases with age (8), and fluctuation in CO_2 tension has been reported to influence the recording of BAEP (1). Preexisting pathology of the auditory system obviously influences BAEP (9,10). The influence of anesthetic agents does not appear to be uniform. Therefore, to allow accurate interpretation of intraoperative changes in BAEP, it is important to delineate the influence of the anesthetic agent being used. Intravenous agents, in particular the barbiturates, are said not to influence BAEP even in the presence of therapeutic barbiturate coma (11). The influence of inhalation anesthetics, however, are not as well defined. Duncan et al. reported that halothane did not influence BAEP in children, but in their study there were no control awake recordings for comparison (5). A small increase in latencies with the induction of halothane anesthesia, therefore, cannot be ruled out, and indeed, James et al. reported a graded increase in latencies of BAEP with halothane in adults (12). Similarly, Dubois et al. found that enflurane significantly increased the latencies of peaks III, IV, and V as well as the interpeak latency I–V (4). Similar results have also been reported by Thornton et al. (13). Stockard et al. recorded BAEP during isoflurane anesthesia, but the influence of isoflurane itself was not delineated (6). We therefore decided to clarify the influence of isoflurane on BAEP in ten normal healthy subjects.

Our stimulating and recording methods were especially chosen to duplicate clinical situations in which rapid repetitive recording and analysis are required. Accordingly, a rate of 21.1 Hz was chosen and 1000 sweeps were averaged. This allows the completion of a recording within 1 min without compromising the quality of the recording as demonstrated by the reproducibility of recordings in every subject.

In our study, we maintained temperature at close to preanesthetic levels by using a thermal blanket as well as warmed intravenous infusion. To further minimize the potential influence of even minor change in temperature, we randomized the sequence of our study so that change due to temperature, which would tend to occur towards the end of the study, would not result in any time-related bias. Moreover, changes in temperature of 0.5°C have negligible effects on latencies of BAEP (14). CO_2 tension was maintained within a very narrow range and monitored closely with the mass spectrometer. All subjects studied were young and healthy with no history of any hearing deficit or neurological disease and all had normal hearing thresholds. Isoflurane anesthesia is associated with a reduction in blood pressure, particularly at high concentrations. To minimize the influence of hypotension on the recording of BAEP, an average of 2500 ml of Ringer's lactate solution was administered to each subject to maintain blood pressure within 75% of preanesthetic value, and in most cases it was within 80%.

In this study we have demonstrated that the effects of isoflurane on BAEP are well defined. The first five peaks were stable and reproducible at each level of isoflurane anesthesia studied. Peaks VI and VII represent cortical responses that can be abolished by nonspecific CNS depressants such as gluthethimide (8,15), and so the latencies of these peaks were not studied in this investigation. At least 15 min of steady end-tidal isoflurane concentration were allowed for equilibration to occur so that a stable brain anesthetic concentration would be achieved. A signficant increase

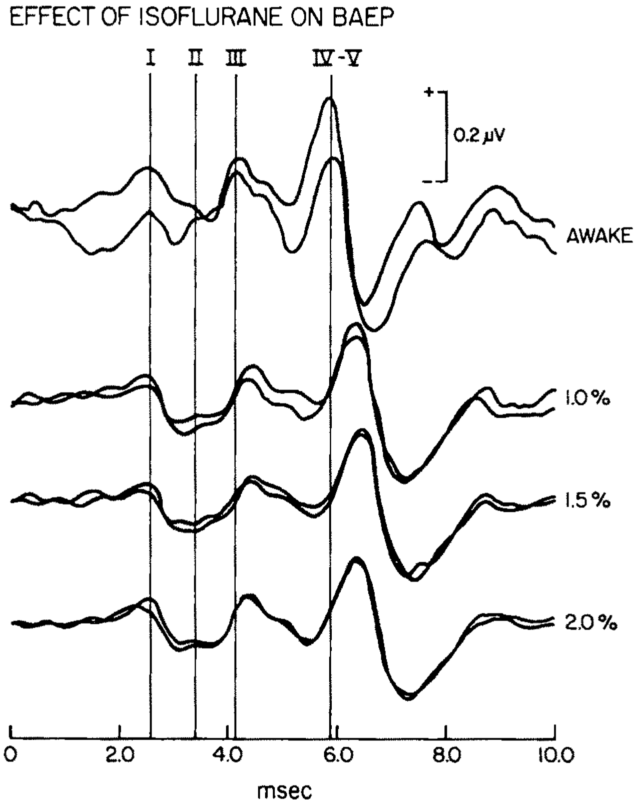

Figure 1. Influence of isoflurane alone on BAEP in a typical subject. Latency of peaks III and IV–V increased at 1.0%, but plateaued with increasing anesthetic depth.

in latencies of peaks III, IV, and V above control awake values occurred at 1.0% end-tidal isoflurane. A slight but nonsignificant increase in latencies was noted from 1.0 to 1.5%, but thereafter there was no further increase in latencies. Thus the influence of isoflurane is self-limiting and there is a plateau effect. This is of clinical importance because deep isoflurane anesthesia has been utilized as a hypotensive agent during neurological anesthesia (16). Delineation of the effect of isoflurane on BAEP allows monitoring of BAEP even during deep isoflurane anesthesia, thereby permitting differentiation between the effects of isoflurane and the effects of potential ischemia. Moreover, the addition of 50% nitrous oxide had no effect on BAEP during isoflurane anesthesia. This is consistent with previous reports by Rosenblum et al. who reported no change in latency with the addition of 70% nitrous oxide to enflurane anesthesia in normal patients (17). However, in patients with certain forms of peripheral hearing impairment, the absolute latencies of BAEP may be increased by the presence of nitrous oxide. This probably occurs as the result of diffusion of nitrous oxide causing an increase in middle ear pressure (17).

The III–V interpeak latency can be defined as the brainstem conduction time. Therefore changes in III–V interpeak latency may be more representative of pathological change than changes in individual peak latencies. The III–V interpeak latency is also relatively independent of variables such as hearing impairment and stimulus intensity and rate (18). Both isoflurane and isoflurane–nitrous oxide anesthesia caused similar significant increases in I–V and III–V interpeak latencies. The plateau effect observed with latencies of individual peaks was also seen with interpeak latencies with, again, no further increases beyond 1.0% end-tidal isoflurane. The increase in III–V interpeak latencies suggests a nonlinear slowing of brainstem conduction with increasing depth of anesthesia.

Analysis of the peak-to-trough amplitudes of the individual peaks showed no consistent or significant change with isoflurane or isoflurane–nitrous oxide anesthesia. This suggests that analysis of peak amplitudes during isoflurane anesthesia may not be useful unless the peaks are abolished.

Although the influence of isoflurane on BAEP is well-defined in the present study, the mechanism whereby isoflurane alters BAEP is far from clear. Similar effects have been reported with enflurane and it has been postulated that they are related to an epileptiform effect interfering with brainstem conduction (4). However, this is an unlikely explanation, because the origin of the epileptic focus is more cortical than subcortical or at the brainstem level. Isoflurane, unlike enflurane, causes no seizure-like activity on EEG recordings in humans, but we have demonstrated that the effects of isoflurane on BAEP are similar to those reported for enflurane. It is likely that the effect of these two anesthetics represents a nonspecific influence of the anesthetics on central conduction as demonstrated by the increase in the III–V interpeak latency. That a plateau effect occurs is not a surprising physiological phenomenon because a similar analogy can be seen in the influence of isoflurane on cerebral metabolic rate (19), which is also nonlinear.

Delineation of the influence of isoflurane on BAEP allows accurate interpretation of intraoperative changes during isoflurane and isoflurane–nitrous oxide anesthesia. Because peak V is the most readily identifiable peak and the influence of isoflurane anesthesia on peak V is well-defined, we have attempted to develop a criterion for the interpretation of intraoperative changes based on peak V latency. Accordingly, we computed the 95% confidence limits for increases in peak V latency due to the influence of isoflurane anesthesia. Because of the plateau effect, we used the increase at 2.0% isoflurane as the basis for our computation. Using this criterion, any prolongation of peak V latency beyond 1 msec from awake control (upper limit of 95% confidence interval) would have to be explained by factors other than a direct effect of isoflurane. Such factors may include the effect of retractors, hypotension, or ischemia to the brainstem. With careful monitoring and interpretation of BAEP, the risk of damage from these manipulations during posterior fossa surgery may be minimized.

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Anesthetic Induction with Fentanyl

Peter L. Bailey, MD, Johan Wilbrink, BS, Prisca Zwanikken, BS, Nathan L. Pace, MD, and Theodore H. Stanley, MD

BAILEY PL, WILBRINK J, ZWANIKKEN P, PACE NL, STANLEY TH. Anesthestic induction with fentanyl. Anesth Analg 1985;64:48-53.

The efficacy of fentanyl, 30 μg/kg, was evaluated as an anesthetic induction agent in 72 ASA I–III patients scheduled for 2–4-hr operations. The effect of preinduction pretreatment with pancuronium and/or diazepam and the incidence of loss of consciousness (anesthesia), recall, rigidity, abnormal muscle movements, and hemodynamic changes were documented. Seventy-four percent of all patients became anesthetized. Diazepam pretreatment enhanced but did not ensure success of anesthetic induction. There was a significant correlation between age and the incidence of unconsciousness (P = 0.0287) and all patients over 60 yr old were anesthetized with 30 μg/kg of fentanyl. The incidence and severity of rigidity was reduced by pancuronium (P = 0.0002) but not by diazepam pretreatment. However, pancuronium plus diazepam produced a significant reduction in the incidence of rigidity when compared to pancuronium alone (P = 0.031). A significant positive correlation between age and the incidence of rigidity (P = 0.003) was found. Six patients had focal and one patient global tonic–clonic abnormal muscle movements. Diazepam but not pancuronium significantly decreased both heart rate (P = 0.05) and blood pressure (P = 0.04). Seventeen patients required reversal of narcotic effect to restore adequate spontaneous respiration after surgery. No patient required postoperative mechanical ventilatory assistance. The results of this study demonstrate that 30 μg/kg of fentanyl is not a reliable anesthetic induction dose in patients less than 60 yr old. Both age and premedication enhance the anesthetic capabilities of induction with fentanyl. However, increasing age is associated with an increased incidence of rigidity and diazepam pretreatment may compromise hemodynamic stability. Significant postoperative respiratory depression can occur with 30 μg/kg of fentanyl used for induction of anesthesia in operations lasting 2–4 hr.

Key Words: ANESTHETICS, INTRAVENOUS—fentanyl. INDUCTION—anesthesia.

Induction of anesthesia with high doses of fentanyl (25–50 μg/kg) and oxygen in patients with cardiovascular disease has been reported to result in a rapid loss of consciousness with little or no hemodynamic alterations, even after laryngoscopy and tracheal intubation (1–6). Although large doses of fentanyl often produce chest wall rigidity during anesthetic induction, may not ensure complete amnesia during operation, and frequently necessitate postoperative mechanical respiratory support, these drawbacks have generally been considered small in comparison to the advantages of fentanyl as an induction agent or complete anesthetic in patients with little cardiovascular reserve. The place, if any, of fentanyl as an induction agent in patients about to undergo 2–4-hr, noncardiac or nonneurologic operations in which subsequent spontaneous ventilation is considered desirable, has not been determined. Therefore, the objective of this study was to evaluate fentanyl as an induction agent in patients scheduled for elective general, orthopedic, or gynecologic operations of less than 4-hr duration. The evaluation was conducted with particular attention to the incidence of rigidity and other abnormal muscle movements, and the incidence of incomplete amnesia after anesthetic induction. Additional observations included the effects of preinduction administration of pancuronium and/or diazepam on rigidity, amnesia, arterial blood pressure, and heart rate during and immediately after anesthetic induction and tracheal intubation, and the need for postoperative mechanical respiratory assistance after operation.

Methods

The study was approved by the Human Ethics Committee of the University of Utah Hospital and Medical School. Informed written consent was obtained from

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Address correspondence to Dr. Peter L. Bailey, Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

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each patient at the time of the preoperative visit. Seventy-two patients between the ages of 18 and 75 served as the experimental subjects. All patients were ASA class I–III and were scheduled for operations lasting at least 2 but not more than 4 hr. No premedication was given. Upon the patient's arrival in the operating room, an intravenous catheter was inserted in a peripheral vein, a standard lead II electrocardiogram was continuously recorded, and a blood pressure cuff was placed on an upper arm for automatic oscillometric blood pressure measurement. After this, patients were given glycopyrrolate (0.2 mg intravenously) and allowed to breathe 100% oxygen for 3 min.

Patients were randomly assigned to one of four groups for anesthetic induction before the preoperative visit by a random number generator. Patients in group I received saline (1 ml) while those in groups II, III, and IV were given diazepam (0.15 mg/kg), pancuronium (0.022 mg/kg), and both diazepam (0.15 mg/kg) and pancuronium (0.022 mg/kg), respectively. Pretreatment medications were given intravenously either 3 min (saline or pancuronium) or 5 min (diazepam) before induction with fentanyl. After this, fentanyl was administered at a rate of 6 μg/kg per min for 5 min.

During infusion of fentanyl, responsiveness to verbal commands was evaluated every 15 sec. Patients were considered unconscious when there was no response to three consecutive commands over a 45-sec interval. If consciousness was not lost after 30 μg/kg fentanyl, 50–75 mg of thiopental was administered intravenously. When absence of response to commands was ensured, the patient was paralyzed with succinylcholine (1.5 mg/kg intravenously) and an endotracheal tube placed in the trachea.

Chest wall rigidity was evaluated during anesthetic induction and before paralysis with succinylcholine by the following scoring system: 0, no rigidity (no difficulty with ventilation during manual positive-pressure ventilation and no clinical evidence of abdominal wall rigidity [palpation] or upper extremity stiffness [manual flexion of the elbow]); 1, mild rigidity (no difficulty with ventilation but some extremity or abdominal wall stiffness); 2, moderate rigidity (some difficulty with ventilation and/or the presence of marked extremity or abdominal wall stiffness); 3, severe rigidity (virtually impossible to ventilate with or without extremity and abdominal wall stiffness). Muscle movements that appeared to be of a tonic–clonic nature rather than simply joint or muscle stiffness were noted and categorized separately as "abnormal muscle movements." Severe, class 3, rigidity was treated with succinylcholine (1.5 mg/kg intravenously) as soon as it occurred while the fentanyl infusion continued. If rigidity did not occur during anesthetic induction, paralysis with succinylcholine and endotracheal intubation was achieved 7 min after starting the fentanyl infusion (2 min after the infusion was concluded).

Systolic arterial blood pressure and heart rate were recorded immediately before pretreatment medication, before beginning the fentanyl infusion, every 2 min during fentanyl infusion, and 1 min after tracheal intubation. Anesthesia was then maintained with nitrous oxide (40–60%) and/or isoflurane (0.25–2.0%) as needed to maintain systolic arterial blood pressure within 20% of preanesthetic values.

During the operation, ventilation was controlled with respiratory rates of 8–14 breaths/min and tidal volumes of 7–12 ml/kg. Muscle relaxation was maintained with pancuronium as clinically indicated. No additional fentanyl, other opioid, or any other intravenous sedative or hypnotic was given for the remainder of the operation. At the conclusion of the operation, patients who had received pancuronium were given atropine, 1.0 mg intravenously, and neostigmine, 2.5–5.0 mg intravenously (depending on thenar or facial muscle responses to train-of-four or tetanic stimulation). Then isoflurane and nitrous oxide were discontinued and the patients ventilated with 100% oxygen for 5 min before mechanical ventilation was terminated. If, 5 min after termination of mechanical ventilation, spontaneous ventilation was not greater than 6 breaths/min, patients were given naloxone in 0.1-mg or nalbuphine in 2-mg increments every 2 min until the respiratory rate was greater than 8 breaths/min. Patients were extubated when tidal volume exceeded 5 ml/kg, respiratory rate was at least 8 breaths/min, and all tetanic and train-of-four evidence of neuromuscular blockade had been antagonized.

Patients were observed for a minimum of 150 min in the recovery room. Naloxone (0.1 mg intravenously) or nalbuphine (2 mg intravenously) was administered if respiratory rate decreased to less than 6 breaths/min or the recovery room nurse observed excessive sedation or renarcotization. The study was concluded when the patients were judged by the recovery room nurse to be adequately recovered from anesthesia to be discharged to their rooms. Patients were interviewed 24–48 hr after the operation and questioned about recall of induction and operative events.

A balanced 2 × 2 factorial design was used to evaluate the effects of pancuronium and diazepam. Statistical software came from the University of California, Los Angeles (7). Data concerning rigidity and

Table 1. Unconsciousness as a Function of Age in 72 Patients Given Fentanyl (30 μg/kg) for Induction of Anesthesia

Age	Rendered unconscious
18–30	57 %
31–45	77 %
46–60	53 %
>60	100 %

$\chi^2 = 4.787$; $P = 0.0287$.

Table 2. Incidence (%) Degrees of Rigidity after 30 μg/kg of Fentanyl in 72 Patients

Pretreatment drug	Number of subjects	Degree of rigidity[a]			
		0	1	2	3
Pancuronium					
No	37	14%	3%	32%	51%
Yes	35	54%	6%	20%	20%
Diazepam					
No	38	32%	8%	23%	37%
Yes	34	35%	0%	30%	35%

[a] 0, no rigidity; 1, mild rigidity; 2, moderate rigidity; and 3, severe rigidity.

unconsciousness were analyzed by stepwise logistic regression analysis, two-way analysis of variance, χ^2 analysis and the χ^2 test for linear trends. Hemodynamic data were analyzed with repeated measures analysis via a multivariate analysis of covariance (with pentothal as the covariate). P values less than 0.05 were considered statistically significant.

Results

There were no statistical differences among the four groups with regard to age, gender, surgical procedure, alcohol consumption, cigarette smoking, narcotic usage, or history of hypertension. Average patient age was 45 ± 16 yr and weight 76 kg ± 23 kg.

Loss of Consciousness and Awareness

Seventy-four percent of all patients (groups I–IV) were rendered unconscious during or two min after infusion of 30 μg/kg of fentanyl. Pretreatment with diazepam before fentanyl significantly increased the incidence of unconsciousness to 88% ($\chi^2 = 7.093$; $P < 0.05$). There was a statistically significant positive correlation between age and the incidence of unconsciousness after 30 μg/kg of fentanyl (Table 1). All patients over 60 yr old lost consciousness with 30 μg/kg of fentanyl whether or not they were pretreated with diazepam (19 patients were over 60 yr old and 10 of these were pretreated with diazepam).

No patient recalled anesthetic induction. Two of 72 patients reported vague recollections of intraoperative events, but without specific recall of pain or conversation. Both of these patients had received diazepam before anesthetic induction with fentanyl. Another patient remembered a wake-up test during instrumentation of the thoracic spine.

Rigidity and Abnormal Muscle Movements

The incidence of any rigidity (the sum of classes 1, 2, and 3 in Table 2) during induction with fentanyl was significantly reduced by pancuronium, from 86% to 46% ($\chi^2 = 14.09$; $P = 0.0002$), but not by diazepam (68% to 65%, $\chi^2 = 0.07$; $P = 0.792$). Pretreatment with pancuronium also significantly reduced the severity of rigidity when it occurred (Table 2). In contrast, diazepam did not change the severity of rigidity. However, patients pretreated with diazepam and pancuronium (group IV) had the lowest incidence of rigidity ($\chi^2 = 4.678$; $P = 0.031$) (Table 3). The increase in rigidity seen with diazepam pretreatment (Table 3), was not statistically significant.

There was a high positive correlation ($\chi^2 = 13.203$; $P = 0.003$) between the incidence of severe rigidity and age (Table 4). Patients under 30 yr old had an incidence of severe rigidity less than 30%, whereas more than 80% of patients over 45 yr old experienced severe rigidity (sufficient to impair adequate ventilation). The time to onset of severe rigidity did not differ among the four groups. The mean time of onset of rigidity was 5.04 ± 0.23 min. Gender, history of narcotic or cigarette usage, and alcohol consumption did not affect the incidence of rigidity. Furthermore, the occurrence of rigidity did not significantly affect systolic blood pressures or heart rates when compared to nonrigid patients.

Seven of 72 patients exhibited abnormal muscle movements that were tonic–clonic in nature and therefore considered to be different than rigidity. Movements were focal (extremity or facial) in six of the seven patients. One patient exhibited tonic–clonic movements in all four extremities and the neck that resembled a grand mal convulsion. At least one patient in each of the four pretreatment groups experienced these abnormal muscle movements.

Hemodynamics

Patients having anesthesia induced with fentanyl alone (group I) or pretreated with pancuronium alone (group III) did not experience significant changes in systolic arterial blood pressure or heart rate during induction or immediately after tracheal intubation (Figure 1). In

Table 3. Incidence (%) of Fentanyl Induced Rigidity as a Function of Pretreatment in 72 Patients

Group	Diazepam	Pancuronium	Rigidity	*n*
I	No	No	60%	(12/20)
II	Yes	No	88%	(15/17)
III	No	Yes	33%	(6/18)
IV	Yes	Yes	18%	(3/17)

Pancuronium: $\chi^2 = 16.729$; $P = 0.000$.
Pancuronium/diazepam interaction: $\chi^2 = 4.678$; $P = 0.031$.

Table 4. Incidence (%) of Severe (Class 3) Rigidity as a Function of Age in 72 Patients after 30 μg/kg of Fentanyl

Age	Rigid
18–30	29%
31–45	59%
46–60	88%
>60	84%

$\chi^2 = 13.203$; $P = 0.0003$

contrast, patients receiving diazepam before anesthetic induction (groups II and IV) had significant decreases in both heart rate and systolic arterial blood pressure (Figure 2). Controlling for a possible effect of thiopental did not change the results.

Postoperative Recovery

Length of operation in this study ranged from 90 to 300 min and averaged 180 ± 36 min. Seventeen of the 72 patients received naloxone (0.1–0.5 mg intravenously) and 11 nalbuphine (2–10 mg intravenously) to antagonize narcotic-induced respiratory depression at the conclusion of operation. All patients were extubated within 30 min of the conclusion of operation and no patient required mechanical ventilatory assistance once in the recovery room. Two patients who had received naloxone showed signs of renarcotization (apnea greater than 20 sec duration) in the recovery room. Both patients responded to verbal stimulation and one additional dose (0.2 mg) of naloxone. Pretreatment with diazepam did not significantly affect the need for a narcotic antagonist.

Discussion

The results of this study demonstrate that 30 μg/kg of fentanyl does not reliably produce unconsciousness (anesthesia) or ensure amnesia in ASA class I–III patients undergoing operations lasting 2–4 hr. The data also indicate that older patients, particularly those over 60 yr old, are more likely to be rendered unconscious with this dose of fentanyl but that they also experience a higher incidence of rigidity. Our findings suggest that preinduction administration of a small dose of pancuronium but not diazepam, reduces the incidence and magnitude of fentanyl-induced rigidity. Curiously, pretreatment with both pancuronium and diazepam results in the most impressive reduction in rigidity. Finally, our hemodynamic data confirm previous studies (1,8) documenting that administration of diazepam immediately before or during administration of a large dose of fentanyl can produce significant decreases in arterial blood pressure and heart rate.

The unreliability of fentanyl as an anesthetic induction agent, particularly in unpremedicated, reasonably healthy patients comes as no surprise to those who are skeptical of opioids as "anesthetics" (9). However, the influence of age as documented in this study and other reports by Berkowitz et al. (10) indicating that older patients sustain higher plasma concentrations of opioids when compared to younger patients, and a recent study documenting significantly higher fentanyl requirements for unconsciousness in patients with histories of smoking and alcohol and caffeine intake when compared to patients without these habits (11), suggest that the dose of fentanyl or any opioid necessary for amnesia and/or complete anesthesia varies markedly from patient to patient. Although it is unclear why habits and age influence blood levels of and anesthetic requirements for fentanyl, a recent study by White and Shafer documents that the problem of predicting dosage requirements for fentanyl is not unique and applies to opioids in general (12). Indeed, these authors found three- to fivefold variations in anesthetic therapeutic serum levels for intravenous drugs of a variety of classes in young (22–25 yr old) women of similar weight and other demographic characteristics.

Although one interpretation of the results of our study and those noted above could be that fentanyl, other opioids, and indeed many intravenous analgesics and anesthetics are unreliable as anesthetic induction and maintenance agents, another might be that predicting correct anesthetic doses of these compounds is difficult, and perhaps, considering all of the information currently available, an inappropriate approach. If this is true, then a more reasonable method of using fentanyl as an induction agent, even if diazepam is part of the induction sequence, would be to give the drug until a desired effect is achieved (unconsciousness, nonresponsiveness to a verbal stimulus, etc.) rather than to give the drug at a fixed dosage, e.g., 30 μg/kg.

The mechanism by which fentanyl and other opioids

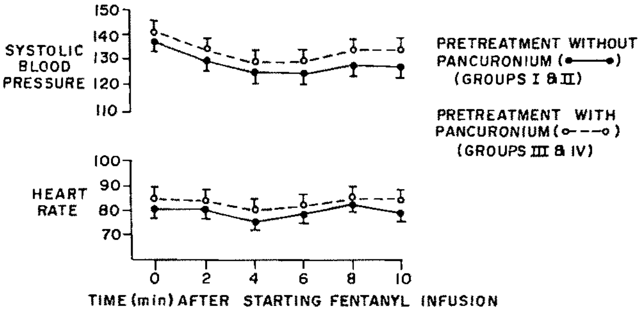

Figure 1. Pancuronium pretreatment (groups III and IV) before fentanyl (30 μg/kg) over 5 min did not cause significant changes in systolic blood pressures (F(1,67) = 2.24; P = 0.14) or heart rates (F(1,67) = 1.66; P = 0.20) when compared to no pancuronium pretreatment (groups I and II).

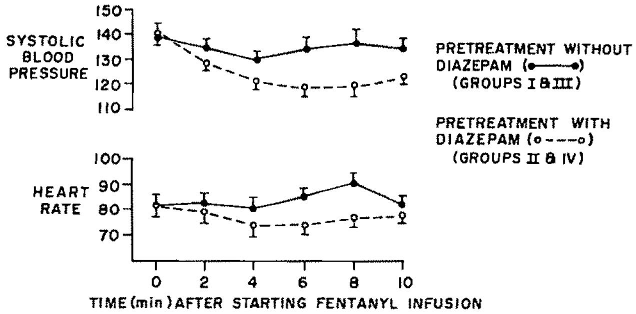

Figure 2. Diazepam pretreatment (groups II and IV) before fentanyl (30 μg/kg) over 5 min caused significantly lower systolic blood pressures (F(1,67) = 4.37; P = 0.04) and heart rates (F(1,67) = 3.95; P = 0.05) when compared to groups I and III without diazepam pretreatment.

produce rigidity in man is unknown. Likewise, methods in which opioid induced rigidity can be attenuated or eliminated have not, with the exception of the use of small or large doses of nondepolarizing relaxants (which prevent the final manifestation of rigidity rather than its causation), had extensive clinical evaluation. Nonetheless there are now numerous animal studies suggesting that opioids induce skeletal muscle rigidity by stimulating opioid receptors. Intrastriatal injections of morphine (into the head of the caudate nucleus) induce muscular rigidity in rats (13) and lesions of the striatum abolish the rigidity induced by systemic administration of morphine (14).

In this study, we found an increasing incidence of rigidity with age. A possible explanation of this finding may be that higher serum (and thus brain) concentrations occur after a given dose of fentanyl in older patients. Also, degenerative changes in the basal ganglia frequently lead to disorders of neuromuscular function (e.g., Parkinsonism) in which rigidity is a common clinical sign. Subclinical changes in function of basal ganglia may predispose older patients to an increased incidence of narcotic-induced rigidity. On the other hand, fentanyl is associated with both an increased incidence of unconsciousness and an increased incidence of rigidity in older patients. This suggests a possible association between rigidity and loss of consciousness. It is possible that rigidity may occur at a stage during a fentanyl (or narcotic) induction during which disinhibition in certain brain areas results in excitatory phenomena that become manifest as rigidity or abnormal muscle movements. Unfortunately, it is not possible to examine either of these hypotheses using our data.

Although GABA agonists/antagonists applied to the substantia nigra can affect narcotic-induced rigidity (15), we did not observe a significant change in incidence or magnitude of rigidity after pretreatment with diazepam (a GABA receptor stimulator). Perhaps the amount of diazepam used in the present study was not large enough to produce a clinically significant GABA stimulatory effect when used alone. Why a combination of diazepam and pancuronium should produce a significant decrease in rigidity as compared with pancuronium alone is also unclear.

Abnormal muscle movements associated with fentanyl induction of anesthesia are not rare and appear to be part of a spectrum of neuromuscular activity extending from mild rigidity to infrequent global tonic–clonic movements resembling a grand mal convulsion. Although some investigators report these events as convulsions or seizures (16,17), human studies fail to document electroencephalographic seizure activity (18,19). The absence of EEG seizure activity does not, however, rule out the possibility that fentanyl may result in subcortical seizure activity not obvious in surface electroencephalograms (20–22).

Absence of significant changes in heart rate and systolic arterial blood pressure during anesthetic induction and tracheal intubation in patients pretreated with pancuronium as compared with patients receiving no pretreatment is not unexpected considering the small dose of pancuronium employed. Our data do not support those who use pancuronium rather than dimethylcurare or *d*-tubocurare as a means for attentuation of rigidity because of the vagolytic qualities of pancuronium. Indeed, the data suggest that 1.5 mg of intravenous pancuronium produces little clinically significant cardiac vagolytic effects.

A surprising finding of this study was the relatively low incidence of troublesome respiratory depression found 2–4 hr after 30 μg/kg of fentanyl. Although 40% (28 of 72) of the patients required naloxone or nalbuphine immediately after operation, only two of these patients required an additional dose of antagonist in the recovery room. That such a relatively high dose of an opioid as potent as fentanyl would produce such an easily managed degree of respiratory depression is a pleasant surprise. On the other hand, while apparently benign, our results might be deceiving. Arterial and/or end tidal P_{CO_2} were not routinely measured in the recovery room. In addition, the close observation and frequent interaction of the investigators and recovery room nurses with the study patients may have partially antagonized fentanyl-induced respiratory depression that may have otherwise been greater if the patients had been left alone.

In summary, 30 μg/kg of fentanyl did not reliably induce anesthesia in ASA I–III patients. Older patients, however, were more likely to lose consciousness with this regimen, and all patients over 60 yr old lost consciousness. Increasing age was also positively correlated with an increased incidence of rigidity. The frequency and severity of fentanyl-induced rigidity was decreased by pretreatment with pancuronium but not diazepam. Diazepam plus fentanyl produced lower blood pressures and heart rates than fentanyl alone or fentanyl plus pancuronium. Postoperative respiratory depression was managed satisfactorily with small incremental doses of narcotic antagonist.

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Flammable Surgical Drapes—A Patient and Personnel Hazard

Ralph A. Milliken, MD, MBA, and Dante V. Bizzarri, MD

MILLIKEN RA, BIZZARRI DV. Flammable surgical drapes—a patient and personnel hazard. Anesth Analg 1985;64:54–7.

After a surgical drape fire, the New York State Society of Anesthesiologists, Operating Room Safety Committee, investigated the factors contributing to it. Subsequently, eight detailed cases were collected. It found that no voluntary standards or government regulations exist to oversee the flammability of surgical drapes; no agency or bureau collects reports of operating room fires; most professionals are not aware of the hazard because no labelling requirements regarding flammability exist and because most episodes are minor in nature or settled out of court and thus not reported. This relatively new hazard has developed with the more frequent use of high-energy devices designed to provide better therapeutic results.

Key Words: COMPLICATIONS—burns, fires. ELECTRICAL SYSTEMS—fires. EQUIPMENT—surgical drapes, fires.

A fire or other combustion event requires oxygen to support combustion, a fuel to be oxidized, and a source of energy for ignition. In the early days of inhalation anesthesia, the anesthetic agents diethyl ether, cyclopropane, divinyl ether, and fluroxene were flammable and explosive because of their relatively unstable molecular structures. The quantity of energy represented by a static electric discharge was adequate to initiate a self-propagating, rapid oxidation event, i.e., a fire or explosion. Oxygen in excess of ambient concentrations always adds to the risk of fire or explosion because it may reduce the required energy level to initiate a self-propagating event and increase the rate of combustion. Nitrous oxide can act as an oxygen provider by degrading into its component molecules. In part because of the dangers of fires and explosions, nonflammable halogenated anesthetics have now essentially replaced older flammable agents.

All fabrics of natural or regenerated cellulose, as well as certain types of finished and unfinished fabrics made from other natural or synthetic fibers (asbestos is classified as a mineral) are flammable. Combustible fabrics, when used for clothing, are potentially dangerous to the wearer. Flammability hazard relates to the speed and intensity of the flame when these fabrics burn, their ease of ignition, or the design of the garment. The following reports illustrate the nature of the hazard of flammable surgical drapes used in the operating room.

Case Report 1

A dilatation and curettage was being performed under general anesthesia. Because of persistent cervical bleeding, the surgeon was utilizing a gauze sponge to help locate the bleeding vessels, and a disposable cautery for hemostasis. The sponge began to smolder and the surgeon threw it to the floor for the circulating nurse to extinguish. The sponge landed on, near or under the disposable surgical drape, which began to burn. The nurse then threw water onto the drape in an attempt to extinguish the fire, but because of the water-repellent nature of the drape, the water helped spread the flames. The nearly explosive rate of combustion caused the leggings of the lithotomy pack to catch fire. Eventually, another member of the operating room team obtained a fire extinguisher from elsewhere in the operating suite and extinguished the flames. The patient suffered first, second, and third degree burns to her perineum and legs, which required skin grafts for therapy (1).

Case Report 2

A 67-yr-old man was sedated prior to being brought to the operating room for a cataract extraction. The anesthesiologist applied appropriate monitoring devices, gave 0.05 mg fentanyl and 5 mg diazepam intravenously and administered oxygen under the dis-

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Address correspondence to Dr. Milliken, Department of Anesthesiology, 234 East 149th Street, Bronx, NY 10451.

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posable drapes. Approximately 6 min after the start of surgery, which included the cauterization of vessels with a disposable hot wire cautery, flames were noted under the drapes. The fire was extinguished, but first and second degree burns developed on the patient's face (2).

Case Report 3

A 4-yr-old girl was receiving general anesthesia with a face mask. Nondisposable cloth was draped to expose a cyst on the patient's forehead. The anesthesiologist was using his left hand to apply the mask to the patient's face. After using a disposable hot wire cautery on a subcutaneous bleeding point, a sterile sponge in the field caught fire. The sponge was thrown to the floor and extinguished by stamping on it, but the drape over the patient's face had already caught fire. This resulted in first and second degree burns to the patient's face and first degree burns to the anesthesiologist's second and third fingers (3).

Case Report 4

During arthroscopy, under nonflammable general anesthesia, a minor surgical delay developed, and the sterile end of the fiberoptic light bundle was removed from the arthroscope and placed on the linen drapes. The light bundle remained attached to the "on" photographic (xenon arc) light source. The drapes immediately began smoking. The fire was quickly extinguished with water. After the event tests were done on drapes of the same type with the same combination of fiber optic carrier and light source. It was verified that the drapes could be ignited in less than one second under identical circumstances (4).

Case Report 5

Dicephalus dipus conjoined twins were individually given general anesthesia for surgical separation. The surgical field was cleansed with a nonflammable antiseptic solution and then draped with a plastic occlusive incise barrier and cotton drapes. The plastic drape encircled the head and neck of Twin A with its adhesive affixed to the extraoral portion of the endotracheal tube. A cone-shaped air space thus existed around the endotracheal tube and the Jackson-Rees modification of the Ayre's T piece used to administer anesthesia. Forty-five minutes into the operative procedure, a blue flame was noted around the electrocautery tip, and the anesthesia circuit connected to Twin A began expelling smoke. All of the tubes that entered Twin A's mouth were burned by the resulting fire. The vital signs of Twin A remained stable for the remainder of the operation until the amputation of Twin A was completed two hours postfire. Full thickness thermal injuries were noted on the face, neck, and part of the thorax of Twin A. Hemorrhagic fluid was present in the alveoli of Twin A, but it could not be conclusively attributed to the fire. Twin B suffered partial thickness burns on her head and along the incision line. She subsequently developed a wound infection, wound dehiscence, septicemia, and a superior vena cava thrombosis. Twin B died on the 46th postoperative day (5).

Case Report 6

A 31-yr-old woman was given endotracheal anesthesia for outpatient laparoscopic tubal cauterization. After successful carbon dioxide pneumoperitoneum had been induced, the left fallopian tube was grasped with a Kleppinger bipolar forceps and the tube coagulated. It was released and grasped again at another segment, but two attempts at coagulation were unsuccessful. After the second attempt it was noted that the disposable surgical drapes were on fire at a point where they touched the cautery cord. All attempts to put out the fire were unsuccessful. The drapes were stripped off the patient while they were still burning and the patient was moved on the operating table to another operating room. The laparoscopic instruments were removed and the incision was repaired.

In the approximate 2 min that it took to move the patient, the entire drape had ignited and filled the room with smoke, making it difficult for the occupants to breathe. The fire was eventually extinguished by the fire department. The patient suffered a second-degree burn to her right hand and a third-degree burn to her right thigh, which later required a skin graft. None of the operating team's disposable gowns ignited during the fire. Inspection of the cautery cord demonstrated that it had melted near the point where it is attached to the laparoscope, a point of considerable torque and stress that probably resulted in a short circuit of the cord (6).

Case Report 7

A patient having a cataract extraction using regional blockade supplemented by neuroleptanalgesia was being administered oxygen by nasal cannulae. A plastic ophthalmic disposable drape was used over cloth drapes to seal the field. Sparking from the cautery during the case set the plastic on fire, causing superficial periorbital burns. Later tests on the plastic and cloth drapes confirmed that cautery in the presence of air would cause the plastic to shrink, but not ignite, whereas when oxygen was present, the plastic and cotton both ignited (7).

Case Report 8

During use of a disposable high-temperature cautery, the "on-off" switch stuck in the "on" position. It was dropped into a fold of the disposable drapes, which promptly ignited. The operating room personnel stripped the drapes from the patient. One surgeon suffered a minor injury in the fire. Inspection of other disposable cauteries revealed that they also had defective switches that continually activated the heating element (8).

Discussion

The ignition source for each of the fires described above, and for those involving surgical lasers (9–11), is a high-energy releasing device that can focus energy onto a small area. These devices are becoming more popular in surgery because of the therapeutic advantages they offer. Their increasing popularity exposes patients to risks most operating room personnel do not recognize.

One of the cases reported resulted in a law suit in which the plaintiff was awarded against the hospital, surgeon, and drape manufacturer. Other cases were obtained from voluntary health sector agencies, which cooperated in varying degrees, and one from a physician's liability carrier, which put us in touch with the individual involved. Our investigations led us to believe that professionals fear publishing reports of operating room fires for concern of possible legal consequences. As a result, there is a limited appreciation of the hazard that patients are exposed to when high-energy releasing devices are used.

In the cases reported above, and in all endotracheal tube fires associated with laser beams, a nonflammable anesthetic agent was used. The fuel was either surgical barrier material and the plastic or rubber materials used in the endotracheal tube, esophageal stethoscope, or intravenous tubing. In some of the reports there exists the possibility that oxygen used to enrich the anesthetic mixture and the patient's ambient gases was available to help propagate the fire.

Anesthesiologists participate in the drafting of flammability standards for some operating room materials and gases through the American Society of Anesthesiologists, Inc., Committee on Equipment, Monitoring and Engineering Technology. Some Committee members participate as members of the Technical Committee on Anesthetizing Agents of the National Fire Protection Association (NFPA), a voluntary, nonprofit corporation formed in 1896 by parties interested in reducing fire hazards. The NFPA does not directly address the flammability of nonwearable product such as surgical barriers. It does have a "Standard for the Classification of the Flammability of Wearing Apparel" (NFPA 702-1970), which tests textiles, and was prepared by the Committee on Fire Tests. The American National Standards Institute has no standard on the flammability of fabrics or wearing apparel.

In 1953 the Federal Flammable Fabrics Act became law. The Secretary of Commerce was made responsible for developing standards for the flammability of clothing textiles. In 1972, the responsibility for flammable fabrics was transferred to the Consumer Product Safety Commission (CPSC). Both the CPSC and the Secretary of Commerce have interpreted their mandate as extending only to wearing apparel, not to other fabrics. Three federal standards have been written for clothing, each relating to the use of the garment and the size of the user. There exists a standard for the flammability of clothing textiles, and two for the flammability of children's sleepwear. Surgical barriers have been considered "internal furnishings," by the CPSC, despite the fact that surgical barriers are temporary wearing apparel for humans of all ages. Surgical drapes, while not tailored as typical garments, are manufactured with fenestrations and apertures to allow the surgeon access to the operative field. We believe that an anesthetized infant or adult is probably at the same or greater risk of fire than a sleeping infant because they are made insensible to the pain of the fire and are unable to act to protect themselves. Recently, the manufacturers of surgical gowns attempted to have the sections regarding surgical gowns (a product the CPSC regulates as wearing apparel) reduced to the weakest flammability standard. If it were not for the fact that many manufacturers use the same material for their drapes as they do for gowns, there would be even less fire protection for patients and personnel.

The US Food and Drug Administration, through the Medical Device Amendments of 1976, became responsible for the development of standards for medical equipment. As of 1983, the Medical Devices Bureau had not developed standards for either surgical drapes or the types of high energy devices involved in the Case Reports and endotracheal tube fires discussed above, despite letters of comment submitted by numerous professional societies and individuals. As a result, there exists no federal reports of operating room fires, and worse yet, no agency that regulates the flammability of surgical drapes.

Prompted by the fire reported in Case Report 2, the New York State Society of Anesthesiologists, (NYSSA) Operating Room Safety Committee, investigated surgical drape fires and found that there was no manner to accurately determine the incidence of operating room fires. In part this is because no central agency or bureau is designated to collect these data, and in part because most cases are settled out of court without any information ever reaching public or professional awareness. As a result, the Committee submitted a resolution that was unanimously adopted by the NYSSA House of Delegates. The Society sent letters to all New York State Congressmen and Senators requesting that they familiarize themselves with the hazard of flammable drapes and seek a solution in federal law. As a result, testimony was given to the House Energy and Environment Subcommittee.

An amendment to the Federal Flammable Fabrics Act was passed by the full Committee and the House. The amendment was attached to the House version of the Consumer Products Safety Amendments of 1983, the bill which would have reauthorized the Consumer Product Safety Commission. The Consumer Product Safety Amendments of 1983 significantly changed many functions of the Consumer Products Safety Commission. The original House and Senate bills varied in their intent and wording. The process of resolving the differences between the two versions is ordinarily the responsibility of a House/Senate Conference Committee. Unfortunately, the Conference Committee never met. With the adjournment of the Congress in October 1984, the two versions of the Consumer Products Safety Amendments of 1983 were lost. It is expected that the wording that mandates a flammability standard for surgical drapes will be part of the original bill introduced in the new Congress in January 1985.

Operating room personnel should consider all types of surgical drapes as potentially flammable, only needing an unfortunate combination of circumstances to result in a fire. Vigilance is required to protect both patients and personnel.

We thank the officers, staff and members of the NYSSA, especially the members of the Operating Room Safety Committee for their assistance.

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Technical Communications

Determination of Atracurium in Plasma by High-Performance Liquid Chromatography

Richard L. Stiller, PhD, Barbara W. Brandom, MD, and David R. Cook, MD

Atracurium besylate is a nondepolarizing neuromuscular blocking agent that under physiological conditions undergoes relatively rapid hydrolysis by nonspecific esterases and by nonenzymatic decomposition (Hofmann elimination) (1,2). Hofmann elimination is enhanced by alkalosis and inhibited by acidosis. Therefore, any assay of atracurium of levels in plasma must be both extremely rapid and at a physiologic pH. Such an assay would be useful in defining the kinetics of atracurium in normal patients of different ages and in patients with severe renal and liver disease. A previously described high-performance liquid chromatography (HPLC) assay for atracurium (3) requires that BW444U, a neuromuscular blocking agent, be added to the glassware to minimize the adsorption of atracurium to the active silanol sites, lacks an internal standard, and lacks sensitivity below 100 ng/ml. BW444U may elute from the HPLC column near atracurium, and thus interfere with the atracurium assay. More important, 4 ml of plasma (about 5.5–7 ml of blood) is required for duplicate atracurium determinations. A biologic assay for atracurium has also been described (2).

To facilitate pharmacokinetic studies in infants and small children, we were interested in developing an assay for atracurium that would minimize the blood or plasma sample required, that would be highly specific, and that would extend the sensitivity below 100 ng/ml. We have refined a highly sensitive HPLC assay that uses either alcuronium or *d*-tubocurarine as an internal standard (4). The sensitivity after extraction of 0.05–0.1 ml (50–100 μl) is 1–2 ng of atracurium. With such an assay we redetermined the effect of pH, temperature, and plasma on atracurium decomposition that had been tested by biological assay (2).

Materials and Methods

We used a Beckman liquid chromatograph (Model 334) with gradient capabilities and with Altec Model 110A pumps, and a Beckman Model 421 microprocessor. The chromatograph was equipped with a Schoeffel spectrofluorometric detector SP-700 P-AL with scan and a Spectra-Physics 4100 microprocessor computing integrating system. Spectrofluorometer was set at excitation wave length of 239.5 nm and at emission of 300 nm. Range setting was 0.02 μA and the sensitivity 550 V. "Little Champ" 7.5 cm, 3-μM, C-18 Regis columns were used as the separation system. Various gradients of phosphate buffers and acetonitrile were used. A 2-μM frit filter was used prior to the column to prevent particle contamination of the stationary phase.

Reagents and Chemicals

In all experiments, highly purified HPLC grade solvents (Burdick & Jackson) or analytical grade compounds were used. Tetramethylammonium hydroxide (TMAH) was a 20% solution in methanol (Aldrich); phosphoric acid was HPLC grade (Fisher). Quaternary ammonium compounds were gifts: atracurium from Burroughs Wellcome Foundation, alcuronium from LaRoche (NJ), and *d*-tubocurarine from Squibb (NJ). The mobile phase was filtered and degassed prior to use. Octadecyl (C-18) extraction columns (Baker) and extraction system vacuum manifold (Baker) were used for separation of drugs. All virgin 5-ml and 1.5-ml conical centrifuge polypropylene tubes were used. All glassware was silanized.

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Address correspondence to Dr. Stiller, Department of Psychiatry, W.P.I.C., 3811 O'Hara Street, Pittsburgh, PA 15213.

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Internal Standards

A solution of alcuronium was prepared in 0.1N HCl (10 mg/10 ml) and a solution of *d*-tubocurarine HCl (1 mg/1 ml) in 0.1N HCl. These stock solutions were stored frozen (−75°C) and were stable for several months; a working solution was prepared from these (500 ng/20 μl).

Preparation of Standards

Immediately prior to use, stock solutions of 1-mg atracurium in 10 ml of 0.1N HCl were prepared; working solutions were prepared from the stock solutions. Different volumes of the working solutions were pipetted into drug-free human plasma. A standard curve was constructed with 1-ml blank plasma samples into 1.5-ml Eppendorf polypropylene conical tubes containing 0, 10, 15, 20, 50, 100, 250, 500, and 2000 ng of atracurium. Each tube contained 500 ng of alcuronium as an internal standard and 20 μl 3N HCl. After thorough mixing on a vortex mixer (10 sec), 500 μl of the sample was placed upon the C-18 extraction column. The samples were extracted by the method described below. Peak heights of internal standard and drug were measured by integration (Fig. 1); the calibration curve was constructed from the peak high ratio of atracurium vs the concentration of the atracurium.

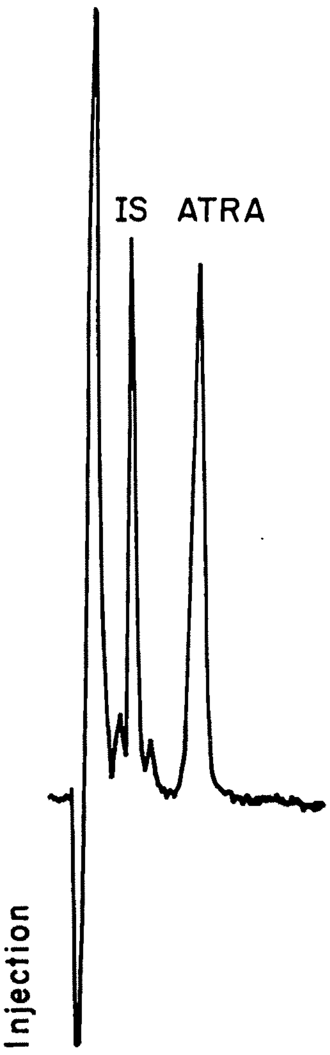

Figure 1. Chromatogram of a mixture of alcuronium, the internal standard (IS), and atracurium (ATA) from a "spiked" plasma sample. The injection time is noted. Retention time is 4.6 min for IS and 9.7 min for atracurium at a flow rate of 0.5 ml/min.

Preparation of Samples

Heparinized peripheral venous blood samples were freshly obtained on the morning of the analysis from volunteers and various amounts of the quaternary compounds and 20 μl 3N HCl were immediately added to them. The blood samples were then centrifuged for 20 sec at 15,000 *g* in an Eppendorf microcentrifuge, Model 5415, and the plasma removed and frozen to −70°C in acetone and dry ice. In addition, arterial blood samples were obtained from a 3-yr-old child 1.5, 3, 5, 7.5, 10, 15, 30, 45, and 60 min after receiving 0.5 mg/kg of atracurium (2 × ED_{95}) during isoflurane anesthesia. The collection of 1-ml blood samples from this patient was in heparinized 3-ml disposable plastic syringes (Becton-Dickinson). The whole blood was squirted carefully into a 1.5-ml polypropylene centrifuge tube containing 20-μl 3N HCl and centrifuged.

Octadecyl C-18 extraction columns were used for separation of the drugs from the plasma. The extraction columns were preconditioned on the extraction system vacuum manifold and under vacuum, the columns were washed twice with methanol, twice with physiological buffer, and a plasma sample of 100–500 μl, including an internal standard, was placed upon the column. These 1-ml columns could not be overloaded or allowed to run dry. The sample on the column was rewashed three times with physiological buffer solution and once with methanol:water (20:80) and the vacuum turned off before the column became dry. The tip of each of the columns was washed clean with buffer and a 1.5-polypropylene Eppendorf centrifuge tube was placed under each column. Then 300–500 μl of eluting solvent, which was in the mobile phase, was added to each column, allowed to stand for a minute, and the vacuum was turned on until the column was dry. Twenty microliters from the eluate was injected onto the HPLC column; with samples containing less than 40 ng, the eluates were dried rapidly in vacuo in a speed-vac concentrator (Savant) and reconstituted with 0.1N HCl.

Procedures

A linearity gradient elution procedure was used to determine what the optimum mobile phase would be for these quaternary ammonium compounds. The appropriate solvent mixture was then established for the assay (i.e., at same flow rate, without variation of the mobile phase proportions). A linear gradient was studied, using a starting mobile phase concentration of 0.03 M TMAH and 0.03 M phosphate buffer (pH 3) in water:acetonitrile (90:10) to the final concentration of the buffer:acetonitrile (10:90).

The appropriate system used was 0.03 M TMAH, 0.03 M potassium phosphate (pH 3), and acetonitrile (60:40) for the separation of alcuronium and atracurium. The column temperature was maintained at ambient temperature, 25°C. The flow rate of 0.5 ml/min was sustained with pressures of less than 1000 lb/in^2. Before injection, the samples were centrifuged at 15,000 *g* to prevent particles from being injected into the HPLC; 20-μl samples were injected. The spectrofluorometric spectrum of alcuronium, *d*-tubocurarine, and atracurium were obtained in an acidic medium. Atracurium has maximum excitations at 280 and 239.5 nm; *d*-tubocurarine at 280 and 240 nm; and alcuronium at 280 and 235 nm.

In a number of experiments, the mean relative net retention time was calculated from the individual retention times. The extraction efficiency of the extraction columns for quaternary compounds was determined with 0.1 ml of plasma samples containing 10-ng *d*-tubocurarine plus 0.10 μCi of ^{3}H *d*-tubocurarine. Also, plasma samples that contained 20-ng atracurium, 500-ng alcuronium, and 20-ng *d*-tubocurarine plus ^{3}H 0.10 μCi *d*-tubocurarine were extracted with C-18 extraction columns and separated by HPLC; 100–500 μl samples were used for the assay. Radioactive atracurium and alcuronium were not available to us.

In pilot studies we added 100–200 ng of fentanyl, morphine, thiopental, ketamine, diazepam, or pancuronium to separate tubes of 1 ml of plasma containing 200 ng of atracurium. Aliquots of this plasma were assayed as outlined above. There was no interference in the atracurium assay from these compounds.

Results

Figure 1 shows a chromatogram of atracurium and the internal standard (IS) alcuronium. The elution sequence (retention time in minutes) was alcuronium, 4.6 min and atracurium, 9.7 min. Laudonosine, one of the metabolites of atracurium, elutes earlier than alcuronium; the alcohol and diol metabolites also elute earlier than atracurium. Total chromatography time between successive samples was 14 min. Plasma concentration of atracurium was determined by comparison of the peak height of the drug and the added internal standard.

Table 1. Degradation of Atracurium

$t_{1/2}$ for atracurium in Sorensen buffer at 25°C, $n = 6$	
pH	$t_{1/2}$ (min)
7.0	160
7.2	140
7.3	98
7.4	73
7.6	54
7.8	42
8.0	26
$t_{1/2}$ for atracurium in human plasma at pH 7.3, $n = 6$	
Temperature	$t_{1/2}$ (min)
37°C	19
25°C	32
5°C	56

Standard curves for atracurium in plasma were linear ($r^2 = 0.998$) from 10 to 2000 ng/ml. Values of atracurium out of this range were either diluted or concentrated and then redetermined. The within-day reproducibility (coefficient of variation %) of the assay determined from five consecutive determinations of 20 or 50 ng of atracurium was 5–6%. The between-day reproducibility (coefficient of variation %) determined on four different days was 6%. Recovery of atracurium ($n = 8$) was 84.4 ± 6% (SD) for the 50-ng/ml samples and 81.1 ± 4.0% for the 20-ng/ml samples.

The degradation of atracurium in Sörensen buffer (reflected by differences in $t_{1/2}$) was more rapid at higher pH (more alkalotic) than at lower pH (more acidotic) (Table 1). At the same pH and temperature (pH 7.3; 25°C) the degradation of atracurium in plasma was three times more rapid than in buffer solution alone (Table 1). The degradation of atracurium was inhibited in plasma at lower temperature.

Figure 2 demonstrates the plasma decay curve of atracurium in a child who had received 0.5 mg/kg of atracurium. This demonstrates the clinical feasibility of the assay. Neuromuscular transmission returns to normal at atracurium concentration of 0.3–0.4 μg/ml.

Discussion

The HPLC method for atracurium is both highly sensitive and selective. The assay sensitivity is much lower

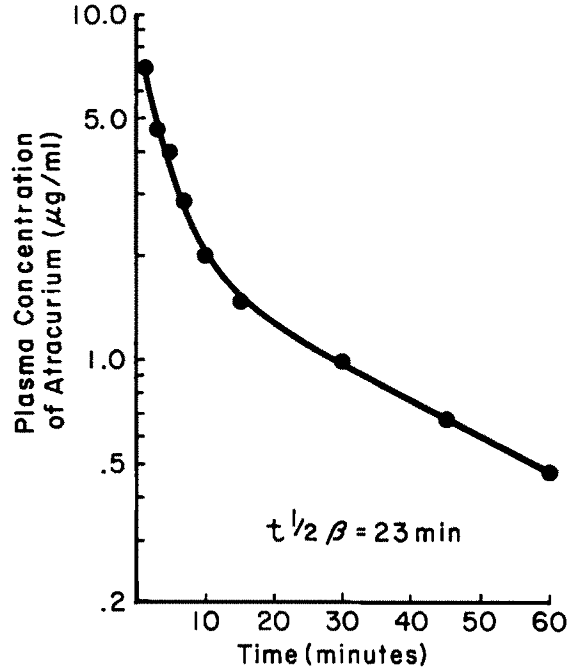

Figure 2. Semilogarithmic plot of atracurium–plasma concentration against time after a bolus intravenous dose of 0.5 mg/kg in a child.

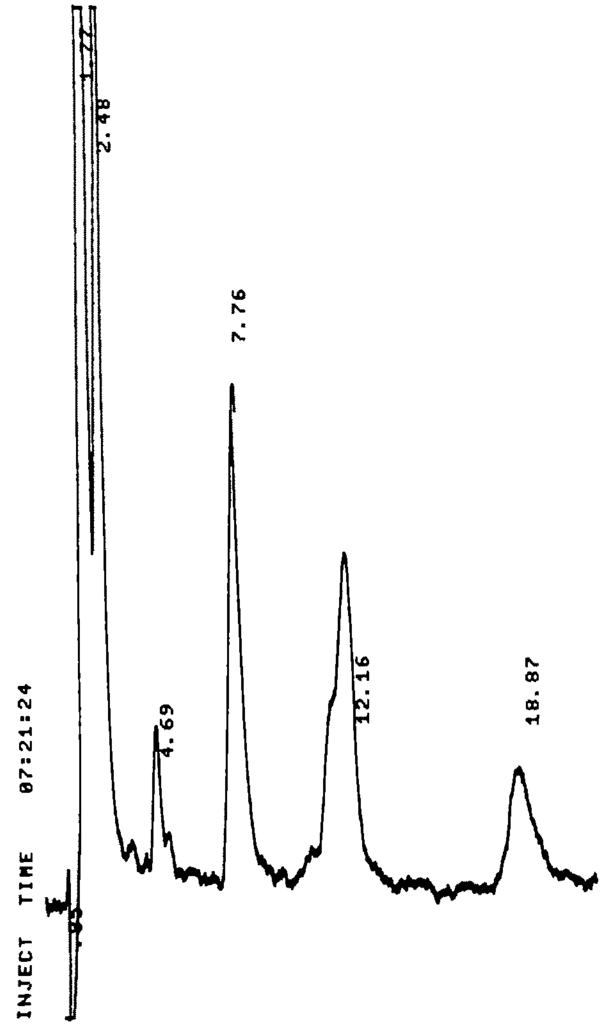

Figure 3. Chromatogram of a mixture of *d*-tubocurarine (20 ng), alcuronium (20 ng), atracurium (20 ng), and BW444U (20 ng) using the described assay. The solvent is the first peak; the relaxants elute in the order listed (left to right). The flow rate is slower than that in Figure 1 to better demonstrate separation of the four relaxants.

than atracurium plasma concentrations associated with clinical neuromuscular blockade (5). The use of an internal standard allows one to control minor variation in the recovery of atracurium during the extraction and separation procedures. Use of polypropylene tubes or silanized glassware eliminated or minimized the absorption of atracurium to glassware. Extraction is performed in a single step with a C-18 extraction column and minimal eluate. Plasma constituents that might interfere with the assay are minimized by the column extraction and further separated from the drug by HPLC using an ion-paired formation reverse phase system.

Quaternary ammonium compounds are irreversibly bound on to the free silanol groups of a reverse phase column in a water–polar organic solvent mobile phase environment. These sites on the reverse phase columns can be deactivated by certain cations at an appropriate pH. Because atracurium and the stationary silica phase are not stable at an alkaline pH, an acidic pH was used to enhance separation, stabilize the atracurium, and overcome the retardive or ion exchange effects of these quaternary bases with the silanol groups on the C-18 column. We were, therefore, able to utilize a C-18 reverse phase column for rapid quantitative analysis of atracurium.

Alcuronium was selected as the internal standard because its structure and retention time on the HPLC are similar to that of atracurium. Of equal importance, there is good separation between the alcuronium and the metabolites of atracurium. *d*-Tubocurarine and BW444U also have retention times similar to atracurium. Thus such an assay may be used by modifying the flow rate to measure these other relaxants (Fig. 3). With further modifications one can measure laudanosine in ng/ml amounts. Because the other metabolites of atracurium are not available, this precludes us from developing a quantitative or qualitative assay for them.

Our assay, like that described by Neill and Jones (3), minimizes the likelihood of atracurium degradation during sample processing. Blood samples are immediately centrifuged; the plasma is decanted, acidified to pH 5, and frozen to −70°C in acetone–dry ice until analysis is performed.

Atracurium spontaneously decomposes through Hofmann elimination to laudanosine and pentamethylene-1,5-diacrylate; nonspecific esterases are responsible for the inactivation of atracurium to a monoquaternary acid and alcohol. Further degradation of the first-split products may take place. In buffer solutions at pH 3.5 and room temperature, atracurium is essentially stable for several weeks; at pH 5–6 it is stable for hours. Our data demonstrate that at physiologic pH in plasma, the degradation of atracurium is extremely rapid when compared to the degeneration in buffer solution alone. Likewise, Merrett et al. (2) noted that the rate of atracurium breakdown in human plasma (at pH 7.2–7.6) was consistently faster by a factor of 1.7–1.8 times when compared with Tris-buffer solutions at the same pH. Absence of pseudocholinesterase has little effect on atracurium metabolism (2). A dual pathway of atracurium degradation does indeed exist. It appears, however, that the metabolism of atracurium by nonspecific esterases is more important than spontaneous decomposition in the degradation of atracurium, and thus in terminating the neuromuscular blocking effects of atracurium. This concept has received little attention. The activity of the nonspecific esterases appears to be inhibited by acidosis and hypothermia. Additional studies will be needed to clarify the role of each pathway in the degradation of atracurium under adverse physiologic conditions.

In summary, we developed a rapid and simple method for the analysis of atracurium plasma concentrations using a high-performance liquid chromatography assay with an internal standard. Total chromatography time between successive samples is 14 min. Recovery of atracurium is about 85%. Linearity over a concentration range of 10–2000 ng/ml is $r^2 = 0.998$. The lowest detection limit of the assay is 2 ng/ml. This method is reliable and sensitive enough for pharmacokinetic use in infants and children.

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On-Line Conjunctival Oxygen Tension as a Guide to Cerebral Oxygenation

Hoyte T. van der Zee, MD, N. Simon Faithfull, MB, PhD, FFARCS, Martin H. Kuypers, Kshetra M. Dhasmana, MD, and Wilhelm Erdmann, MD, PhD

A need exists for continuous on-line measurement of arterial oxygen partial pressure (Pa_{O_2}) in the critically ill patient. The method should preferably be noninvasive and the apparatus needed should be compact and simple to operate.

Since the introduction of the first membrane-covered polarographic cell (1), oxygen polarography has undergone such refinement that P_{O_2} measurements can now be carried out with great accuracy in almost any situation. Measurement of respiratory gas tensions in blood are routine, but the intermittent and invasive nature of the estimations has prompted the search for other, preferably on-line, measurement techniques.

Continuous transcutaneous monitoring of oxygen tensions has gained considerable popularity and is widely practiced in the neonatal period (2). This method has also been employed in adults (3), but it has been shown that, although transcutaneous oxygen tension reflects the Pa_{O_2} in patients with a normal cardiovascular status, this is not necessarily so in shock and low flow conditions (4).

It has been pointed out (5) that a particularly suitable position for sensing oxygen tension is to be found in the palpebral conjunctiva, because it possesses a dense capillary bed that assists in the oxygenation of the cornea, when the latter is not exposed to the surrounding air. It is, therefore, not surprising that the conjunctival capillaries are located very close to the surface layers, hence minimizing the distance over which oxygen must diffuse.

By application of solid state technology, it has been possible to produce a miniature membrane-covered polarographic Clark cell. A low cost, mass produced, O_2 sensor chip has recently been produced by Honeywell Medical Electronics (6), and this paper reports our initial laboratory experiences with this device. The in vivo performance and the correlation between measured P_{O_2} values and those obtained from the arterial blood are reported, together with comments on the sensor's response characteristics under various hemodynamic conditions.

Methods

The Conjunctival Oxygen Sensor

A diagrammatic representation of the sensor is presented in Figure 1. The principle of the ring-shaped cathode system (7) was incorporated by constructing two rectangular spirals (8). In this manner it was possible to combine the small width of the cathode (which determines the sensitivity of the polarographic cell to flow) with a relatively large total cathode area, and thus stronger electrode current. This has several advantages, such as small zero current and improved stability—two factors that are difficult to achieve in miniaturized microelectrodes.

The gold cathode and the silver anode are vapor-deposited on a silicon substrate, while a silicon–oxide layer is used for insulation between the electrodes. A porous cross-linked polymer matrix between the cathode–anode system and the rubber membrane serves as carrier for the electrolyte. The polymer matrix, the electrolyte, and the membrane are all applied by spin coating. The electrode is activated just before use by equilibrating in saline. This procedure has several advantages, but it obviously restricts applicability of the cell for the measurement of oxygen in a completely fluid medium.

The cable is only 140 μm in diameter, protected by a Teflon tube, and fastened to the chip by ultrasonic bonding techniques. The dimensions of the chip are

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Address correspondence to Dr. Faithfull, Department of Experimental Anaesthesia, Erasmus University, 3000 DR Rotterdam, The Netherlands.

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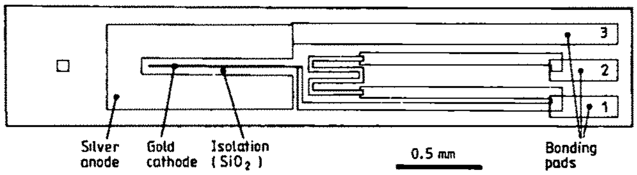

Figure 1. Diagrammatic representation of the subconjunctival polarographic oxygen sensor.

0.7 mm × 3.7 mm and it has a thickness of 0.4 mm. The whole is embedded in a flap of silicon rubber in such a way that the membrane of the chip is in direct contact with the inner-surface of the eyelid. This flap is 45 mm long, 4 mm wide, and 0.5 mm thick, thus enabling it to be fixed directly onto the skin adjacent to the eye. The soft surface of the pliable rubber is in contact with the eyeball, so there is no danger of damaging the surface of the eyeball.

The electrode has a high sensitivity of approximately 250 pA per mm Hg change in Po_2, which results in an oxygen consumption of 1.5×10^{-11} ml of oxygen per mm Hg. Prior to application, the O_2 sensor was calibrated in 0.9 NaCl equilibrated with air. The electrode current was fed into a Philips XV 1506 amplifier system, and conjunctival oxygen tension was continuously recorded using a Philips PM 822 pen recorder.

Experimental Studies

The studies were performed in Wistar rats anesthetized with halothane in 33% oxygen and 66% nitrous oxide. The O_2 sensor was applied between upper eyelid and cornea, the chip facing the palpebral conjunctiva. The eyelid was then closed to ensure a tight apposition of the sensor to the conjunctival tissues.

The femoral artery was cannulated with a 1-mm external diameter polythene cannula. This was connected to a Gould P23 pressure transducer, and after amplification by a Grass 7B polygraph, systemic arterial pressures were recorded on a Grass ink-writing oscillograph. Blood was intermittently withdrawn from the arterial cannula for measurements of blood–gas tensions using a Radiometer ABL 1 acid–base laboratory. The ECG was monitored continuously.

The animals were ventilated via a tracheostomy with 0.5% halothane vaporized in a nitrous oxide–oxygen mixture. The Loosco Amsterdam infant ventilator was adjusted to achieve normal end-tidal CO_2 values, as measured on a Godart type 1467 capnograph. Muscular relaxation was achieved using pancuronium bromide, administered as a continuous infusion via a Braun Melsungen Perfusor apparatus at a rate of 0.4 mg/hr.

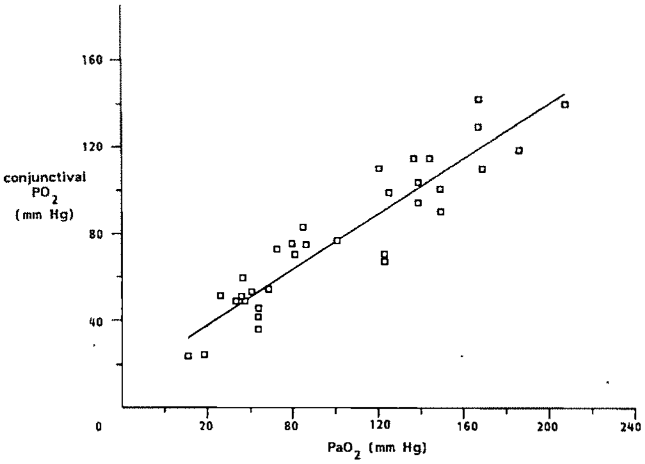

Figure 2. The relationship between arterial oxygen tension (Pao_2) and conjunctival oxygen tension. The regression line is drawn in. The correlation coefficient is 0.93.

The inspiratory oxygen concentration ($\mathrm{FI}_{\mathrm{O}_2}$), measured using an Instrumentation Laboratory Oxygen Monitor 404, was varied between 0.2 and 0.5. Arterial blood samples were taken for blood–gas analysis at the end of a 15-min period of ventilation at each $\mathrm{FI}_{\mathrm{O}_2}$.

The O_2 sensor was then tested for its response characteristics during normo- and hypovolemic hypotension. Normovolemic hypotension was induced by ventilating with 4% halothane and by injection of ketamine hydrochloride (1 mg/kg) into the cisterna magna. Hypovolemic hypotension was induced by withdrawal of blood from the femoral artery.

In some animals, both common carotid arteries were exposed. After baseline conjunctival Po_2 (Pcono_2) readings were established, the left carotid was occluded with an arterial clamp. After a new steady-state Pcono_2 was established, the arterial clamp was released. This procedure was repeated on the right side. After a recovery period, simultaneous bilateral clamping was performed.

Results

The sensor was stable for extended periods of time, both in vitro and in vivo. In Figure 2, the values of arterial oxygen tension (Pao_2) are plotted against the simultaneously measured conjunctival oxygen tensions obtained in each animal subjected to various $\mathrm{FI}_{\mathrm{O}_2}$ values. The regression line is indicated and there is a good overall correlation, with a correlation coefficient of 0.93 ($n = 33$). The conjunctival Po_2 appears to give a better indication of Pao_2 in the normal and hypoxic range than in the hyperoxic range of arterial oxygen tensions. Although in both instances the cor-

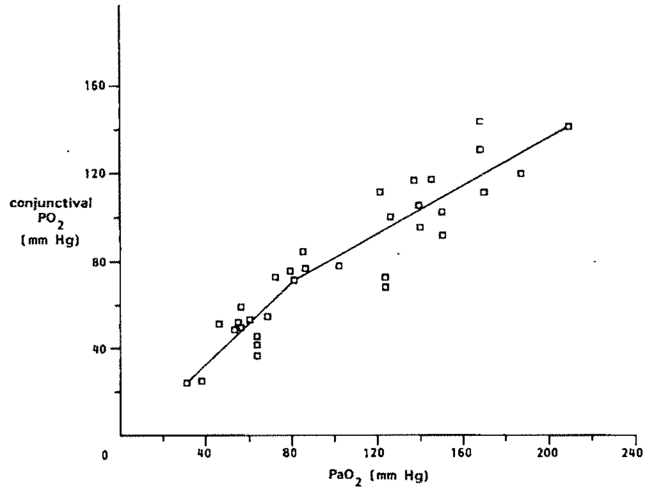

Figure 3. The relationship between arterial oxygen tension (Pa_{O_2}) and conjunctival oxygen tension. The regression lines are drawn for Pa_{O_2} values of 100 mm Hg and below and for 100 mm Hg and above. Correlation coefficients and slopes of the regression lines are discussed in the text.

relation coefficient is 0.81 (this is statistically significant), the slope is 0.93 in the lower range but only 0.55 in the hyperoxic range (Fig. 3).

Recordings of $Pcon_{O_2}$ obtained during stepwise changes in $F_{I_{O_2}}$ are shown in Figure 4. The changes in oxygenation of the conjunctival tissue are rapidly detected by the O_2 sensor and after about 10–12 sec, stable readings are obtained at the new P_{O_2}.

The effects on hyperventilation, hypoventilation, and temporary apnea are demonstrated in Figure 5. Hyperventilation, induced by an increase in the tidal volume, results in an increase in $Pcon_{O_2}$, reflecting improvement of tissue oxygenation. However, continued hyperventilation does not maintain this improvement in oxygenation of the conjunctival tissue, and one can observe a slow decline to below the original baseline level. This may be the result of the vasoconstrictive effect of low carbon dioxide tensions on the cerebral circulation (Pa_{CO_2} decreased from 50 to 20 mm Hg). It is interesting to note that this effect reached a maximum value and was followed by a slight increase in conjunctival P_{O_2} reading. Possibly this may indicate an altered vascular response to very low Pa_{CO_2} (hypoxic vasodilation). Also demonstrated in this figure is a temporary apnea producing an immediate decrease in $Pcon_{O_2}$. After hyperventilation, the animal was hypoventilated, resulting in a Pa_{O_2} of 39 mm Hg and a Pa_{CO_2} of 60 mm Hg. An immediate decrease of the conjunctival P_{O_2} value was seen, followed by a slow increase that was probably due to the vasodilatory effect of the increasing Pa_{CO_2}.

Figure 6 demonstrates the responses of the O_2 sensor after injection of ketamine into the cisterna magna, the intravenous infusion of 0.9% saline solution and the withdrawal and subsequent reinfusion of blood. It can be seen that $Pcon_{O_2}$ closely parallels the ensuing changes in mean arterial pressure.

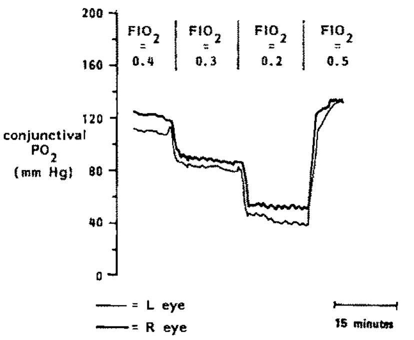

Figure 4. Responses of the subconjunctival oxygen sensor to stepwise alterations in fractional inspired oxygen concentrations ($F_{I_{O_2}}$).

In Figure 7 the effects of halothane-induced hypotension on $Pcon_{O_2}$ are illustrated together with subsequent changes produced by intracisternal ketamine. The decrease in conjunctival P_{O_2} after halothane was clearly less than that observed during ketamine-induced hypotension of similar magnitude. This is probably due to the potent vasodilatory effect of halothane, which might be expected to maintain better microcirculatory perfusion during severe hypotension.

Figure 8 shows results obtained during studies on the effect of occlusion of the common carotid arteries. Clamping of the left carotid resulted in a considerable reduction in the ipsilateral $Pcon_{O_2}$. Almost identical decreases were produced by clamping the right common carotid artery. Simultaneous bilateral clamping of the carotid arteries produced a much more dramatic decrease in $Pcon_{O_2}$ to clearly hypoxic levels. The latter indicates a severe reduction in cerebral blood flow, prevented during unilateral clamping by the presence of an intact anterior communicating artery.

Discussion

The solid state O_2 sensor used in our experiments proved to be a reasonably accurate sensor of the state of conjunctival tissue oxygenation, and there was a fairly high correlation between $Pcon_{O_2}$ and Pa_{O_2}. It could be postulated that the lower correlation between the $Pcon_{O_2}$ and Pa_{O_2} in the hyperoxic range could be explained on the basis of the presence of autoregulatory vasoconstrictive mechanisms similar to those occurring in the cerebral circulation. This would appear reasonable considering the anatomical origin of the opthalmic circulation.

In practice, a very useful feature of the O_2 sensor is its rapid response time (10–20 sec). An early con-

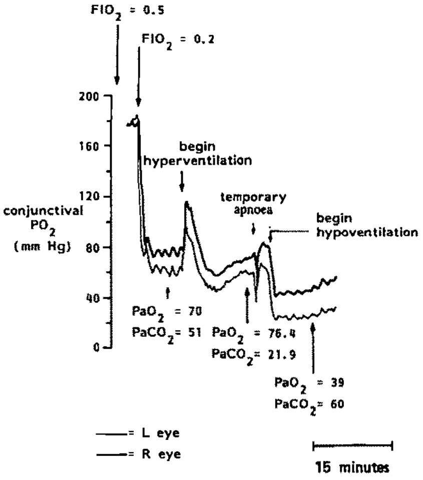

Figure 5. The effects on subconjunctival oxygen tension of hyperventilation, apnea, and hypoventilation.

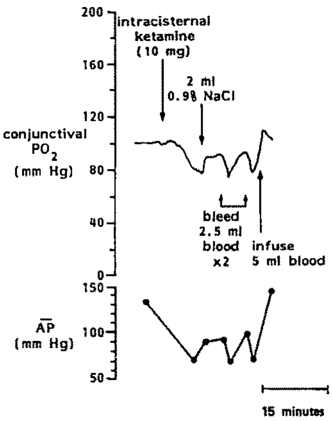

Figure 6. The influence of intracisternal ketamine, intravenous administration of 0.9% NaCl, bleeding and reinfusion of blood on the mean systolic pressure (AP), and on conjunctival Po$_2$.

junctival electrode (5) had a response time of as long as two minutes, and was therefore unsuitable for detection of rapid acute changes in Po$_2$. The electrode that we used is thus much more suitable, and changes in tissue oxygenation, secondary to changes in oxygen flux, can be rapidly and accurately assessed, allowing rapid therapeutic intervention in clinical situations. The clinical use of a conjunctival Po$_2$ electrode has recently been described (9), but no mention of response speed was made. Although Pcono$_2$ was always lower than Pao$_2$, the sensor was able to follow the trend of the changes in arterial oxygen tension.

No specific studies have yet been carried out to investigate the effect of anesthetic agents on this electrode system. Studies into the effect of halogenated agents have been carried out in the past (10) and halothane has been shown to be the anesthetic agent in common use that has the most effect on readings obtained from standard Po$_2$ electrodes. Comment was made that ". . . the errors involved are small in most instances." Enflurane and isoflurane were shown to have no effect on Po$_2$ measurements. The authors observed a slow upward drift of Po$_2$ readings in the presence of halothane. This was not observed in the present study, and therefore the effect of halothane in the anesthetic gases respired by the animals was probably not significant.

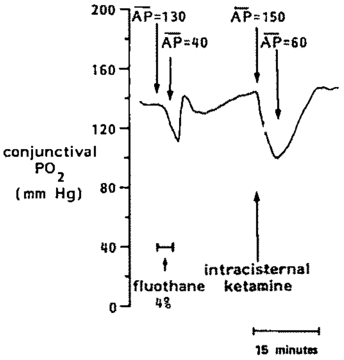

Figure 7. The influence of ventilation with 4% fluothane or intracisternal administration of ketamine on the arterial pressure and on the subconjunctival Po$_2$.

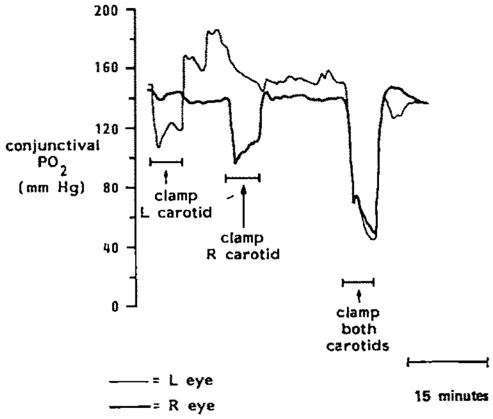

Figure 8. The effects on the subconjunctival Po$_2$ of clamping one or both common carotid arteries.

The ciliary artery, which supplies the conjunctiva, carries blood coming from the internal carotid artery. It should thus be possible to gain some idea of the adequacy of the cerebral circulation by the use of bilateral conjunctival oxygen electrodes. This should increase the margin of safety during, for instance, surgery for the relief of partial obstruction of the carotid artery. The instrument may also find useful application in neurosurgical practice, where it might give early warning of vascular compression or of vascular insufficiency during clamping of cerebral aneurysms. In addition, the sensor may be used as a research tool for investigating pharmacological action of drugs on the cerebral vascular smooth muscle.

The manner and the degree to which the sensor responds to alterations in PaO_2 and hemodynamic conditions suggest that the electrode is reflecting changes in cerebral oxygen flux. It has been maintained (11) that a change in the oxygen carrying capacity of the blood has no effect on the $PconO_2$. However it is quite possible that after hemodilution with low molecular weight dextran and consequent lowering of the blood viscosity, the cardiac output of the experimental animals (rabbits) was increased to the extent that total cerebral oxygen flux was unchanged. It is therefore important to perform further experiments to ascertain whether indeed a relationship exists between the output from our electrode and cerebral oxygen supply. This would be particularly valuable in view of the enormous clinical importance of such a measurement.

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Clinical Reports

Intraoperative Use of Verapamil for Nitroglycerin—Refractory Myocardial Ischemia

Linda S. Humphrey, MD, and Thomas J. J. Blanck, MD, PhD

Nitroglycerin (TNG) is currently the mainstay of acute cardiac ischemia therapy. While there is some controversy about the precise mechanism of its beneficial effect, it is clear that TNG rapidly aborts many ischemic episodes. Occasionally a situation is encountered in which chest pain or ST segment changes suggesting ischemia persist despite seemingly adequate TNG therapy. In the past two years, we have treated four such patients with intravenous verapamil and describe a representative case here. We have found verapamil to be rapid in onset and effective, both as an adjunct to other interventions and in the face of ongoing ischemia refractory to usual therapeutic measures.

Case Report

A 70-yr-old man with triple vessel coronary artery disease was scheduled for urgent coronary artery bypass surgery. Angina had been present for many years and he had sustained two myocardial infarctions ten and fifteen years earlier. This hospitalization was precipitated by persistent chest pain at rest. He was admitted to the coronary care unit, infarction was ruled out, and treatment was instituted with intravenous TNG and oral nifedipine with abatement but not resolution of his symptoms. Cardiac catheterization demonstrated total occlusion of the left anterior descending (LAD) and left circumflex arteries with retrograde filling of the LAD and circumflex marginal from the right coronary artery, which itself had a high grade stenosis. Overall left ventricular function was fair with a stroke volume of 56 ml, an ejection fraction of 0.47, and a left ventricular end diastolic pressure of 7 mm Hg, which increased to 16 mm Hg after ventriculography.

After premedication with morphine sulfate (8 mg intramuscularly) and scopolamine (0.3 mg intramuscularly), the patient was brought to the operating room. Peripheral intravenous lines, a radial arterial line, and a pulmonary artery catheter were introduced. Intravenous nitroglycerin was continued at a rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Initial hemodynamic studies showed the left ventricular function was satisfactory with a cardiac index (CI) of 2.5 $L \cdot min^{-1} \cdot m^{-2}$ and a left ventricular stroke work index (LVSWI) of 42 $g\text{-}m \cdot m^{-2} \cdot beat^{-1}$. A baseline 12-lead ECG was recorded and was unchanged from previous tracings, showing only nonspecific ST-T wave changes.

Anesthesia was induced with diazepam and fentanyl followed by pancuronium for muscle relaxation; intravenous TNG was continued throughout. Ventricular function and ECG were unchanged after induction and intubation. Diazepam (10 mg) and nitroprusside (75 μg) were administered just prior to sternotomy but despite this, the systemic blood pressure increased to 160/75 mm Hg and the heart rate (HR) to 75 beats/min from previous levels of 123/50 mm Hg and 64 beats/min, respectively. Shortly thereafter, 3 mm of ST depression was noted in multiple leads and the pulmonary artery diastolic pressure increased from 14 to 25 mm Hg. The CI decreased to 1.96 $L \cdot min^{-1} \cdot m^{-2}$. The nitroglycerin infusion was in creased to 4 and then 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, sublingual TNG 0.4 mg was given, and the systemic pressure was quickly controlled with small bolus doses of nitroprusside. Ten minutes later, the systemic blood pressure was 115/64 mm Hg, the HR 74 beats/min, the pulmonary arterial pressure 70/35 mm Hg, and the ST segments still depressed (Fig. 1). Verapamil (7.5 mg intravenously) was given in three

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Address correspondence to Dr. Humphrey, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, MD 21205.

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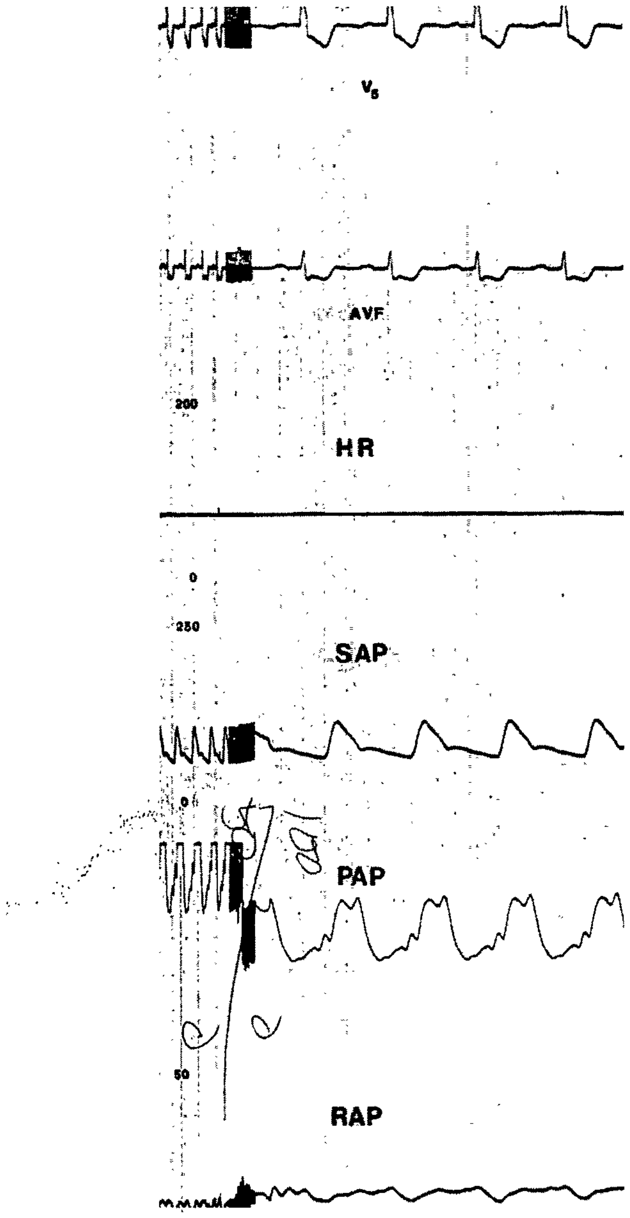

Figure 1. ECG and hemodynamics during intravenous nitroglycerin, taken from continuous intraoperative 8-channel recording. V_5, V_5 chest lead ECG (top tracing); AVF, AVF lead (second tracing); HR, heart rate, beats/min, recorded on a 0–200 scale; SAP, systemic arterial pressure, mm Hg, recorded on a 0–250 scale; PAP, pulmonary arterial pressure, mm Hg, recorded on a 0–100 scale; and RAP, right atrial pressure, mm Hg, recorded on a 0–50 scale.

divided doses over a 5-min period. Within 1 min after the full 7.5 mg dose was complete, the ST segments were returning to baseline, and the pulmonary arterial pressure was beginning to decrease, first to 65/26 mm Hg and then, 3 min later, to 54/22 mm Hg. The HR decreased to its previous level of 65 beats/min (Fig. 2). Bypass was instituted and terminated uneventfully; neither inotropic support nor pacing was required and left ventricular function remained good

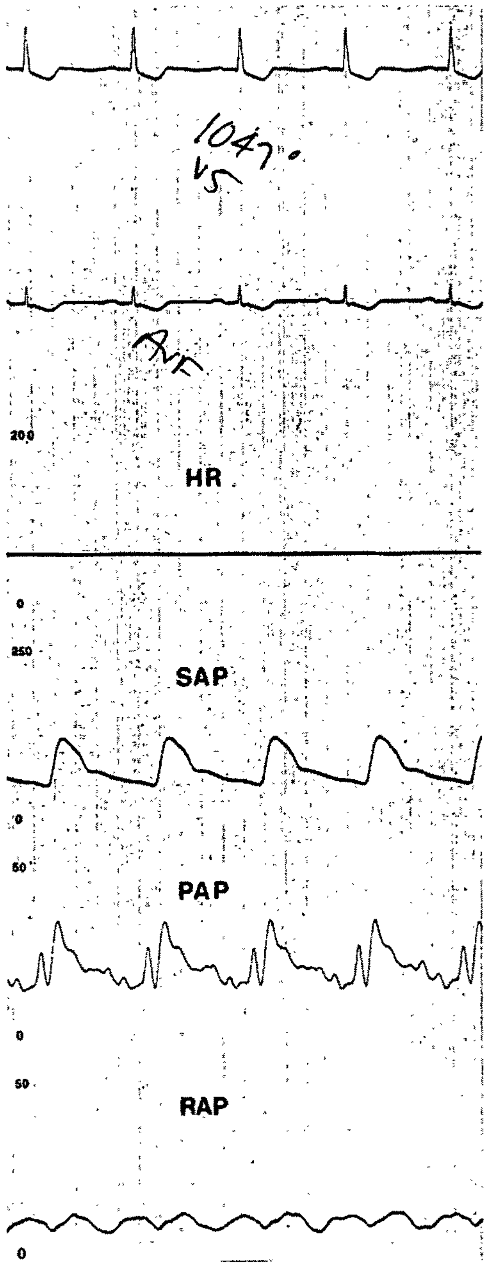

Figure 2. ECG and hemodynamics after verapamil (7.5 mg intravenously). Abbreviations and notations as in Figure 1, with the exception of pulmonary arterial pressure, which is now recorded on a 0–50 scale.

during the postoperative period. There was no evidence of myocardial infarction or other problem related to the ischemic episode.

Discussion

The efficacy of the calcium channel blocking agents (CCBs), verapamil, nifedipine, and diltiazem, in the treatment of angina pectoris has been established for Prinzmetal's angina in which vasospasm plays a major role (1–6). Recent evidence suggests that CCBs are also effective in patients with classic exertional angina and rest angina associated with depressed ST segments (5–7). Because the mode of action of the CCBs is believed to be related to their ability to relax vasospastic coronary arteries (3,5,8), the fact that they are also effective in forms of angina that have been assumed to be related solely to fixed coronary lesions suggests three possibilities: classic angina might have a vasospastic component, the CCBs have a second mode of action, or both. In fact, vasospasm of major coronary arteries has been demonstrated in patients with subtotal coronary lesions (9,10) and is felt to play a significant role in the development of so-called unstable, accelerated, or preinfarction angina (3,6,11). Furthermore, the CCBs have several hemodynamic actions beside coronary vasodilation that could contribute to their beneficial effects in the treatment of classic angina (5,6,8). Kates and Kaplan found decreases in systemic vascular resistance, systemic arterial blood pressure, and LVSWI in eight coronary bypass patients given verapamil (0.075 mg·kg^{-1}) during narcotic-based anesthesia (12). Others have seen a decrease in HR after verapamil in dogs anesthetized with volatile agents (13,14) and in awake, β-blocked humans (15).

Several factors have contributed to the relatively infrequent use of verapamil for the chronic treatment of patients with angina as compared to the other CCBs. The extensive metabolism of verapamil by the liver limits its oral effectiveness (5,6,8). The depressant effect of verapamil on the SA node and conduction system (5,8,11,16,17) has resulted in concern about its use in combination with β-blockade (3,5,11,18). Verapamil is also believed to possess a more potent negative inotropic effect than the other CCBs (6,8) that is accentuated in patients with reduced ventricular function (5,19).

In the perioperative period, many of the characteristic effects of verapamil cited above may be used to advantage. The rapid onset and short half-life are clearly beneficial for intravenous treatment of ischemia. At present, verapamil is the only CCB available in this country for parenteral administration, eliminating uptake from oral or sublingual sites as a factor in onset of action. SA node inhibition resulting in decreased HR and decreased inotropy both contribute to reductions in oxygen demand. These factors make verapamil an attractive choice for perioperative use in combating ischemia in patients with good ventricular function. Although it is impossible to know whether vasospasm played a contributing role in the ischemic episode in our patient, use of verapamil was definitely associated with a decrease in myocardial oxygen demand.

The potential problems associated with intravenous administration of verapamil include inordinate decreases in contractility with significant hemodynamic impairment and the development of varying degrees of AV block. The former problem did not arise in our patient and tends to occur either in patients with severely compromised ventricular function or at high dosage levels (6). In fact, in some of our patients, we have seen increases in CI after verapamil, presumably resulting from reduction in afterload, improvement in function as ischemia was alleviated, or both. The problem of AV block is also dose related and can be avoided by carefully titrating the drug to effect. Verapamil should not be used in patients with known impairment of conduction (6,11).

It is unclear why TNG was ineffective in alleviating ischemia in the present case and in the other cases we have encountered. Maximal coronary vasodilation may have been achieved with TNG prior to the ischemic attack; verapamil administration may then have decreased contractility and heart rate while maintaining coronary and systemic vasodilation. Alternatively, the blood level of nitroglycerin might have been inadequate to reverse coronary spasm. Intracoronary nitroglycerin may be required to achieve this (20). A third possibility is that adsorption of TNG by the infusion tubing might have reduced the actual dose of TNG administered. This seems unlikely because the infusion had been running for several hours and producing hemodynamic effects, suggesting that tubing binding sites were already saturated.

Use of oral CCBs to treat TNG-refractory ischemia is commonplace outside of the operating room. In addition, Hasin et al. reported 16 patients with postinfarction angina treated with continuous infusions of verapamil for 36–48 hr (21). Fourteen remained pain free during the infusion, while only two extended their infarcts. Similar treatment of intraoperative TNG-refractory ischemia with intravenous verapamil seems logical, but has not been previously described.

Nifedipine, on the other hand, has been used in several instances. Buxton et al. described six patients with coronary spasm after bypass, manifested by ST segment elevation and hemodynamic collapse, who were unresponsive to intravenous TNG (20). Three died and two were reversed only by intracoronary TNG. Five of the six were administered nifedipine via nasogastric tube but no parenteral CCB was given. Another case of coronary spasm after bypass reported by Lewis et al. was reversed after sublingual TNG and nifedipine (22). Improved coronary graft flow and contractility occurred over 15–25 min. This compares to 6 min in our case from the initial dose of verapamil to the onset of improvement in ST segments and 10 min to the time when ST segments had returned to baseline. Two other instances of reduced graft flow after bypass were treated with direct intracoronary injection of nifedipine (23). This modality produced rapid improvement but is presently available in this country only on an experimental basis. Thus verapamil is not necessarily superior to the other CCBs in correcting ischemia, but the rapidity of onset with intravenous administration is an advantage.

There may be several reasons why verapamil has not been used previously to treat intraoperative ischemia. The hemodynamic effects of verapamil in combination with general anesthetics have only recently been delineated, eliminating concern about its intraoperative use (12,14,24). Also, because many coronary bypass patients are β-blocked, the administration of intravenous verapamil to them may have seemed unwise. The combination of oral β-blockers with small doses of intravenous verapamil has not produced the higher degrees of AV block seen when both are given intravenously.

In summary, we present a case of perioperative ischemia that was well controlled by verapamil after nitroglycerin alone proved inadequate. It is unclear whether verapamil reversed coronary spasm in this episode or whether its major effect may have been to decrease myocardial oxygen demand by decreasing contractility, maintaining decreased afterload, and slowing HR. Because verapamil is fast, effective, and safe for ischemia of either etiology, its use should be considered when ischemia develops during the perioperative period.

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Fentanyl Anesthesia in Familial Dysautonomia

B. Beilin, MD, Ch. Maayan, MD, E. Vatashsky, MD, D. Shulman, MD, I. Vinograd, MD, and
H. B. Aronson, MB, ChB, FFARCSDA(I)

One of the uncommon but serious problems that the anesthetist may face is the inherited disease familial dysautonomia (FD), a multisystem disease, most of the clinical manifestations of which are related to pathology in the nervous system (1). There is a reduction in the number of cells in the autonomic and sensory ganglia and a decreased number of unmyelinated and myelinated fibers. Norepinephrine and epinephrine excretion is diminished, although metabolites of dopamine are excreted in normal amounts. During emotional crises, nevertheless, plasma norepinephrine and dopamine levels are markedly elevated, with smaller increases in epinephrine (2,3). Clinically, patients with FD have difficulty in swallowing, vomiting (dysautonomic) crises with dehydration, poor control of body temperature, and generally decreased perception of pain but with some areas of hyperesthesia (4). Especially important for the anesthetist is marked cardiovascular instability that may manifest itself by episodes of orthostatic hypotension or attacks of hypertension, as well as hypersensitivity to exogenous catecholamines (5,6). These patients require special attention from the anesthetist during surgery because their clinical status may deteriorate due to the stress of the perioperative period.

The anesthetic management of patients with FD, as described by several authors (5–8), is based on the cautious use of volatile anesthetics together with exogenous catecholamines in order to provide stability of the cardiovascular system. In most of the patients described, there were, however, marked changes in blood pressure during surgery and the postoperative period. The search, therefore, continues for an anesthetic technique that produces a more stable hemodynamic status.

Anesthesia with high doses of fentanyl (HDF) is not associated with a sympathoadrenal discharge and may, in critically ill patients, even prevent the sympathoadrenal response to surgical stimulation (9). Moreover, HDF has been shown to block other hormonal stress responses, such as the secretion of antidiuretic hormone, cortisol, growth hormone, and insulin (10,11).

The success of HDF for open heart surgery led us to consider use of this method for patients with FD. The present report describes our experience with a moderate-dose fentanyl technique in these very difficult patients.

Patients and Methods

Six procedures were performed under general anesthesia on four patients (2 males, 2 females, aged 1.75–23 yr) who were admitted to our hospital with previously diagnosed FD (Table 1). All suffered from recurrent pneumonias, motor retardation, and psychoemotional imbalance. Most of the classical symptoms and signs of FD (12) were present, including lack of superficial sensitivity to pain, orthostatic hypotension, and attacks of vomiting and hypertension. Gastric reflux was documented by barium swallow and milk scan. Intensive preoperative preparation with chest physiotherapy, deep suction, antibiotics, and cimetidine were administered before surgery. Gastrostomy was performed in all four patients. Three patients underwent elective Nissen fundoplication, in which the fundus of the stomach was sutured around the esophagus as a "collar" creating a new gastroesophageal valve (13). In one patient who had severe chronic lung disease from recurrent pneumonias, tracheostomy was performed one week prior to the surgical procedure, and bronchography was carried out postoperatively for evaluation of lung pathology.

Premedication consisted of sedation alone for two reasons: sedative drugs may prevent or minimize psychoemotional crises; and standard doses of narcotics can be dangerous in these patients because of their sensitivity to hypercarbia and hypoxemia. Thus on

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Address correspondence to Dr. Beilin, Department of Anesthesia, Hadassah University Hospital, Mount Scopus, PO Box 24035, Jerusalem, Israel 91240.

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Table 1. Characteristics of the Patients with Familial Dysautonomia

Patient no.	Sex	Age (yr)	Weight (kg)	Height (cm)	Procedure	Duration of procedure (min)	Recovery time from end of procedure till extubation (min)
1	M	8	14.4	98	Gastrostomy plus fundoplication	150	360
2	M	4	12	84	Tracheostomy	30	240
2	M	4	12	84	Gastrostomy plus fundoplication	130	480
2	M	4	12	84	Bronchography	110	180
3	F	1.75	5.7	66	Gastrostomy	60	840
4	F	23	30	110	Gastrostomy plus fundoplication	140	720
Mean		9.2	15.5	89.5		103	470

the morning of surgery, the patients were premedicated orally with either diazepam or flunitrazepam in the doses previously found to be suitable (Table 2). They were brought to the operating room with a previously inserted intravenous infusion. A pediatrician was in attendance from the time of administration of premedication until the patient's arrival in the operating room.

Anesthesia was induced with either flunitrazepam (0.01 mg/kg) or diazepam (0.1 mg/kg) given in diluted form intravenously over a period of 2 min. This was followed by an infusion of fentanyl (30 μg/kg) and pancuronium (0.1 mg/kg) in a volume of 5 ml/kg of Ringer's lactate solution. Half of this solution was infused over the first 10 min followed by tracheal intubation. The remainder was given prior to the commencement of surgery. Oxygen was given initially by a mask positioned above the patient's face while, after induction, an oropharyngeal airway was inserted and a tight fitting face mask applied for spontaneous and then assisted ventilation. When the eyelash reflex was obtunded and controlled ventilation became necessary, nasotracheal intubation was carried out. The nasal route was chosen to facilitate postoperative ventilation that was planned for all patients because of the high narcotic dosage used during anesthesia.

After tracheal intubation, rigidity of the chest wall, a possible side effect of HDF, was evaluated by the degree of resistance to manually controlled ventilation. The internal jugular vein and the radial artery were then cannulated, and a urinary catheter and rectal temperature probe inserted. Patients were warmed in the operating room by a radiant warmer and thermal blanket. ECG was continuously displayed and systolic, diastolic, and mean blood pressures were monitored (Syntron automatic blood pressure recorder). Central venous pressure (CVP), end tidal CO_2 tension, ($Petco_2$) (Datex capnograph), and arterial blood gas tensions were also measured frequently during the perioperative and early postoperative periods.

Anesthesia was maintained with a 50:50 N_2O:O_2 mixture administered by manual ventilation through a T-piece (Jackson-Rees modification of the Ayer's T-piece). Additional fentanyl (200 μg boluses) was given intravenously during the procedure whenever systolic blood pressure or heart rate, or both, increased more than 15% above the preanesthetic control values. If this supplement failed to reduce systolic blood pressure within 5 min, 0.3% halothane was given until the systolic pressure decreased to control levels. This was needed in only one case and for a total duration of 5 min.

Special attention was given to fluid balance. Because these patients are generally hypovolemic and hypoalbuminemic from repeated vomiting, they received 10 ml/kg of fresh frozen plasma (FFP) in the evening prior to surgery. This was repeated before induction of anesthesia together with the above-mentioned Ringer's lactate solution 5 ml/kg. During anesthesia and surgery Ringer's lactate solution was given at a rate, usually 10 ml·kg^{-1}·hr^{-1}, sufficient to maintain a urinary output of at least 1 ml·kg^{-1}·hr^{-1}, and the CVP within the normal range. Blood was available for replacement on a unit-for-unit basis.

At the end of the surgical procedure, the patients, while being manually ventilated, were transferred to the intensive care unit without reversal of either fentanyl-induced respiratory depression or of residual muscle relaxants. Patients were ventilated (Bennett MA-2) with up to 5-cm H_2O positive and expiratory pressure followed by intermittent mandatory venti-

Table 2. Drugs and Doses Administered During the Perioperative Period in 4 Familial Dysautonomia Patients (6 interventions)

Patient	Surgery						ICU		
no.	Diazepam	Flunitrazepam	Fentanyl	Pancuronium	FFP	Bicarbonate	Meperidine	Flunitrazepam	Diazepam
1	5 mg	0.4 mg	600 μg	2 mg	400 ml		45 mg	0.3 mg	17.5 mg
2	5 mg	0.1 mg	50 μg	3 mg		15 mEq	40 mg	0.4 mg	
	10 mg		450 μg		200 ml	15 mEq	30 mg	0.2 mg	5 mg
		0.1 mg	200 μg	2.2 mg				0.2 mg	5 mg
3		1.0 mg	200 μg		200 ml		15 mg		5 mg
4		0.4 mg	1100 μg	4 mg	400 ml		60 mg	0.8 mg	

lation (IMV) until such time as spontaneous ventilation was adequate to permit extubation of the trachea. This was performed from 4 to 14 hr after surgery. During the postoperative period, the patients received 1 mg/kg of meperidine intramuscularly every 3 hr for analgesia and diazepam or flunitrazepam intravenously to reduce the stress of mechanical ventilation, to prevent psychoemotional crises, and for their antiemetic effect. When all vital signs were stable, the patients were transferred to the ward. Informed consent was obtained for this study from the adult patient and from the parents of the children.

Results

All four patients were calm and sleepy on arrival in the operating room and cardiovascular findings were similar to those obtained during the preoperative preparatory period (Fig. 1). During induction of anesthesia there was a transient decrease in systolic blood pressure (mean 23% decrease) that was reversed by increasing the infusion rate. With the start of surgery, one patient had a further decrease in blood pressure that was reversed with FFP administration. In a second patient there was a blood pressure increase of approximately 30% that rapidly returned to normal after an additional dose of fentanyl (200 μg) and a 5-min administration of 0.3% halothane.

Heart rates before induction of anesthesia were generally rapid (95–140 beats/min) but were slower (70–100 beats/min) during the course of surgery (Fig. 1), except for patient 3, aged 1.75 yr, whose heart rate remained elevated during surgery. For most of the operative period, changes in blood pressure and CVP were unusual and tended to parallel alterations in heart rate, although there were some instances in which this link was not apparent. These changes were responsive to adjustment of the rate of fluid administration. Thus we found that added fluids increased all three variables, heart rate, blood pressure, and CVP, at the same time. These variables were generally stable throughout the operative and postoperative periods.

Repeated measurement of blood gas tensions and $\mathrm{Petco_2}$ showed no changes indicative of hypercarbia or hypoxemia, $\mathrm{Paco_2}$ varied between 4.4 and 6.3 kPa, and $\mathrm{Pao_2}$ varied between 11.5 and 20.7 kPa. The mean arterial pH decreased from 7.40 to 7.32 by the end of the procedures, and, in two of the six interventions, the base deficit increased to 8.8 and to 10.1 mmol/L, respectively, necessitating bicarbonate administration. Chest wall rigidity was not detected at any time, nor was there any difficulty in ventilating these patients throughout the procedure.

No exogenous catecholamines were found to be necessary in any patient. The additional doses of fentanyl and pancuronium administered during surgery did not amount to more than 25% of the initial doses (Table 2). The fundoplication procedures were of approximately the same duration in all three cases (Table 1), and blood loss was minimal so that there was no need for blood transfusion. The immediate postoperative course was very satisfactory and patients were fully conscious within 6–8 hr of the end of the surgery. Ventilation and IMV were well accepted by all patients and weaning was gradual and uneventful. The time to endotracheal tube extubation ranged from 4 to 14 hr. Meperidine and the benzodiazepines were well tolerated (Table 2). There were no hypertensive or vomiting crises. When questioned postoperatively, none of the patients reported experiencing awareness or pain during the procedure.

Discussion

Patients with FD can be compared to those with cardiac disease before open heart surgery from the point of view of their severe cardiovascular instability and the pathological changes in the sympathetic and peripheral nervous systems. In both groups, marked cardiovascular changes both pressor and depressor that can result from the reflex response to endotra-

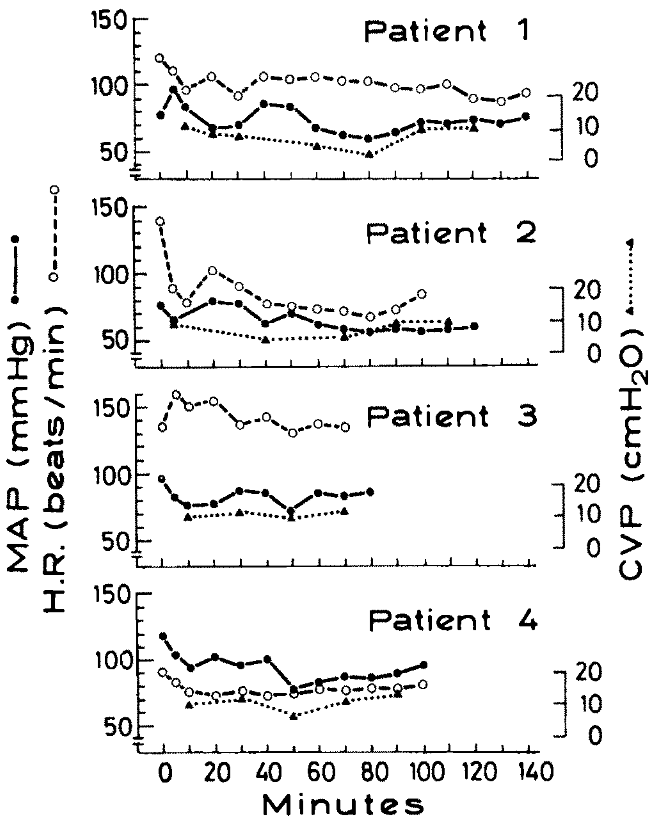

Figure 1. Mean arterial blood pressure, heart rate, and central venous pressure changes during anesthesia in four patients with familial dysautonomia.

cheal intubation and surgical stimulation may be dangerous or even fatal. The ideal induction agent for the patient with FD should, therefore, provide for pleasant loss of consciousness, produce minimal cardiovascular disturbance, and cause no side effects. Patient apprehension is a major destabilizing factor in these patients and should be controlled in the preoperative period.

Several anesthetic techniques have been proposed for patients with FD (5–8). Anesthesia based on inhalational agents such as halothane or enflurane has been used, but may induce hypotension due to myocardial depression and peripheral vasodilation, necessitating the administration of exogenous catecholamines. However, patients with FD are extremely sensitive to even small doses of epinephrine, which may induce cardiac arrhythmias and uncontrollable hypertension. Myocardial depressants are thus not advisable. For this reason, and given the difficulties in predicting an appropriate dose, thiopental, if used at all, should be administered in small amounts.

Because of the problems associated with inhalation anesthesia in patients with FD, we were interested in an alternate anesthetic technique that would provide cardiovascular stability without myocardial depression. The results achieved with the moderate-dose fentanyl technique that we used in this small group of patients with FD are encouraging. The patients arrived in the operating room with stable cardiovascular findings after heavy premedication with benzodiazepines and fluid therapy designed to rapidly load the intravascular compartment. The infusion of 15 μg/kg of fentanyl and 1–2 mg of pancuronium provided smooth induction without chest rigidity and allowed easy intubation and ventilation. The additional dose of 15 μg/kg of fentanyl given before and the 200 μg administered intermittently during surgery probably suppressed any significant changes in cardiovascular dynamics. The intermittent use of low concentrations of halothane as a supplement during hypertensive episodes proved very satisfactory in the one patient who required it, without causing sudden hypotension. The fact that elevations in blood pressure occurred together with a decrease in heart rate, indicated to us that baroreceptor reflexes were not intact.

The dominant risk factors in patients with FD, namely hypertension or hypotension, vomiting, and pulmonary derangement from repeated respiratory infections, make postoperative ventilation mandatory. Thus the necessity to ventilate after this moderate-dose fentanyl anesthesia is not a disadvantage of the technique, and the postoperative sedation it confers is a distinct advantage in these patients. Recovery of consciousness is smooth and return to spontaneous ventilation is gradual without distress.

We are fully aware of the possible criticism concerning the use of moderate doses of fentanyl for relatively short diagnostic or therapeutic procedures, but the stress of even a short operation can be marked and deleterious to these patients and must be avoided. The question arises whether it is preferable to treat the stress responses simply by increasing the dose of analgesic drug to an undefinable level of analgesia, or to use higher doses of hypnotics, such as the benzodiazepines. Further studies are planned in these patients with cardiovascular, central nervous system, and metabolic monitoring, including estimation of plasma catecholamine levels.

In conclusion, we have described an effective and apparently safe anesthetic technique based on the use of moderate doses of fentanyl and intensive monitoring for patients with FD undergoing diagnostic procedures, major surgery, or both. Our results indicate that cardiovascular parameters intra- and postoperatively were stable, and the postoperative period was relatively smooth without hypertensive or hypotensive episodes. While we cannot claim that this technique is superior to the other accepted methods of anesthesia, because a controlled comparative study was not performed, it is our clinical impression that the moderate-dose fentanyl technique described provides the basis for safe anesthesia for patients with FD.

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Halothane or Enflurane for Inhalation Induction?

A Study of Children's Preferences

Eamon Tierney, MB, BCh, FFARCSI, Peter A. Ritchie, MB, BS, BSc, FFARCS,
William R. Hain, MB, BS, FFARCS, and Richard A. Cooke, MB, BS, BSc, FFARCS

The introduction of enflurane prompted many reports on its clinical use, a high proportion comparing the effects with those of halothane. Pediatric anesthetists were not slow in publishing their experiences with enflurane. Rodrigues (1) described the use of enflurane in pediatric anesthesia in 1973. Govaerts and Sanders (2) compared halothane and enflurane in pediatric anesthesia and found more rapid induction and recovery times with enflurane. Black et al. (3) found the mean induction time for enflurane to be two-thirds that of halothane, with an equally rapid recovery time. A discouraging note was that occasional difficulties were encountered in very small children when using enflurane as the induction agent. Black et al. postulated that respiratory depression may occur before surgical anesthesia has been achieved. Davidson (4), comparing halothane and enflurane in pediatric anesthesia, found similar induction times for the two agents. She postulated that the quicker recovery time after enflurane anesthesia was due to the fact that the enflurane-treated patients received a less potent anesthetic dose, taking the different MAC values into consideration. She commented on the acceptability to children of enflurane for inhalation anesthesia.

Many children in our practice choose an inhalational induction. This investigation sought to establish, therefore, whether children have a preference for either the smell of halothane or enflurane, in a belief that it would be more humane to use the preferred agent, if any, where clinical considerations would recommend either equally. Ethical permission was obtained for a double-blind trial.

Material

A cotton-wool ball (250 mg approximately) was placed into a number of amber glass bottles, of approximately 10-ml capacity, numbered but otherwise identical. Either halothane or enflurane (0.5 ml) was put into each bottle in a random fashion. The code as to which bottle contained which agent was known only to the pharmacy, and was kept in sealed envelopes in the pediatric induction room (the code was to be broken if a child expressed a definite preference for a particular numbered bottle, and that agent was then used for the child's induction). One hundred twenty-five children, five years or older, scheduled for anesthesia on the next day, and without previous experience of anesthesia, were included in the study.

Method

A bucket of coded bottles, in jumbled array, was brought by the resident pediatric anesthetist on his preoperative visit. Each child was asked to choose two bottles at random. Each child was asked to open a bottle and sniff its contents. After thirty seconds, he or she was asked to open the other bottle. On each occasion, his or her reaction was noted and was placed by the observer in one of the categories "like", "accept", "reject". The child was then asked which bottle he or she preferred, which was recorded (a definite preference, no preference, or no difference detected). The observer stood at a distance from the child, which did not permit him to detect which agent was contained in either bottle.

Results

Table 1 shows that each bottled agent was assessed individually and then compared with the second bottle chosen by the child. Table 2 shows that of the 250 bottles offered to the children, 129 contained halothane and 121 contained enflurane. We see that half the children liked the scent, one-quarter rejected it,

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Address correspondence to Dr. Hain, Children's Intensive Care Unit, University Hospital, Queen's Medical Centre, Nottingham, NG7 2UH England.

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Table 1. Example of the Forms Used in the Study Detailing the Exact Words Spoken to the Child and Showing the Method of Recording the Results

Name Number Date	Bottle no.	Rejects	Accepts	Likes
I want you to choose two bottles from this bucket. Now open one and sniff it. Now close it. (Wait thirty seconds.) Now open the other one and sniff that. OK Now close that.				
Which smell did you like best, the first bottle or the second?	1	2	No preference	"Same smell"

Table 2. Results Showing Childrens' Opinions of the Scents Presented to Them and Demonstrating the Numbers of Bottles Containing Either Halothane (H) or Enflurane (E) Chosen

	"Likes"	"Accepts"	"Rejects"	
E	58 (47.93%)	35 (28.92%)	28 (23.14%)	121
H	65 (50.38%)	34 (26.35%)	30 (23.25%)	129
Total				250

Table 3. Results Obtained in the Four Possible Permutations of Scents Chosen Showing the Children's Preferences, if any, for Halothane (H) or Enflurane (E)

H + E	E + H	H + H	E + E
13 preferred H	10 preferred E	12 preferred 1st	10 preferred 1st
9 preferred E	6 preferred H	13 preferred 2nd	9 preferred 2nd
4 "no preference"	1 "no preference"	2 "no preference"	2 "no preference"
8 "the same"	8 "the same"	9 "the same"	9 "the same"
Total 34	25	36	30

and one-quarter were equivocal, whether the agent was halothane or enflurane.

Of the 66 children who received similar bottles (Table 3), 22 preferred the first bottle, 22 preferred the second bottle, and 22 had no preference or thought they were the same. The order of presentation, therefore, did not affect the preferences expressed.

Of the 59 children who received both scents (either halothane followed by enflurane or enflurane followed by halothane), 23 preferred the first scent, 15 preferred the second scent, and 21 had no preference or thought they were the same. Applying a statistical nonparametric sign test to these results, we find that the apparent preference, at first glance, for the scent in the first bottle offered is not statistically significant.

Applying a χ^2-test (4 degrees of freedom) to the tabulation of results in Table 4, and taking as the test hypothesis that a patient has some preference for either halothane or enflurane there is no reason to reject the null hypothesis ($\chi^2 = 2.149$; $P = 0.29$).

Taking the figures in the right column of Table 4, we find an apparent preference for halothane. Applying a nonparametric sign test (two-tailed) to these figures, we find we can reject the hypothesis that the apparent preference for halothane is statistically significant.

Discussion

Two conclusions are possible from the results obtained in this study. First, enflurane and halothane have odors that are indistinguishable to children. This is refuted by common experience. Second, neither agent has a more generally acceptable odor than the other. This would appear to dispel the myth that the odor of enflurane, being an ether, is more pungent than that of the hydrocarbon, halothane. Thus the decision as to which of the anaesthetic agents should be used need not be influenced by considerations of patient acceptability generally.

Table 4. Summary of Results Showing Preferences, if any, for Halothane (H) or Enflurane (E)

	H + H	E + H	H + H or E + E	
Preferred H	13	6	25	44
Preferred E	9	10	19	38
"No preference"/"the same"	12	9	22	43
Total	34	25	66	125

However, individual patients may express very marked preferences for one or the other agent. In another group of children requiring multiple brief anesthetics, gas mixtures containing enflurane and halothane were presented and a preference sought. Although this was an uncontrolled study open to observer bias, it is interesting that these knowledgeable, experienced children also show a preference for one, another, or neither agent in approximately equal proportions (WR Hain, unpublished observations).

Toward the end of the 6-week period of the trial, some children volunteered that there was no odor from a chosen bottle. These children were excluded from the trial. Our pharmacist studied this apparent loss of agent with time and concluded that loss does occur from the bottles, more quickly from the bottles containing halothane than those containing enflurane. However, the effect was marginal at room temperature, and differences between the two agents became significant only when the bottles were refrigerated. He found that the mean loss after 28 days at room temperature was 13.3% for both halothane and enflurane. This had no apparent effect on detection of the odor.

Of the 66 children who sniffed the same agent twice, 44 (two-thirds) expressed a preference for either the first or the second bottle. Conversely, of the 59 children who sniffed both agents, 21 (approximately one-third) either had no preference or thought they were the same.

One advantage of conducting this study was that in those children who expressed a preference, anesthesia was induced with their preferred agent. We had the strong clinical impression that, possible because the children had experienced the anesthetic odors beforehand, inhalation induction was often suprisingly calmly accepted by the child. A willingness to establish and allow the child his preferences may, in this as in other aspects of induction, assist both patient and anesthetist.

In summary, a double-blind trial was conducted in which 125 children were asked to sniff bottles containing a small amount of either halothane or enflurane. No apparent general preference was expressed for either agent by the group of children, although some individuals had decided preferences. Decisions as to whether to administer halothane or enflurane in children should, by and large, be based on factors other than patient preference because there is no significant preference among children for either. This study dispels the myth that a halogenated ether, in the form of enflurane, is more pungent than the hydrocarbon, halothane.

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Prolonged Myoclonus after Etomidate Anesthesia

Thomas P. Laughlin, MD, and Leslie A. Newberg, MD

Etomidate (a carboxylated imidazole derivative) is a new ultra-short-acting hypnotic induction agent that provides several advantages for use in high-risk patients. Induction with etomidate with a single bolus injection is characterized by the rapid onset of hypnosis within 1 min and a duration of action of 3–5 min (1). There is no tolerance or cumulation effect with repeated administration because etomidate is rapidly metabolized in the liver to inactive compounds (2). Etomidate does not cause histamine release (3) and maintains cardiovascular stability during induction in healthy patients (4–6) and in patients with cardiac disease (7,8).

Reported side effects of etomidate noted during induction include pain on injection (20%) (9,10), apnea lasting 5–90 sec (11), and myoclonia (36%) (9,10). Although the myoclonia may resemble convulsive seizures, it is not considered hazardous and appears to be a manifestation of disinhibition of subcortical structures (12). In this it resembles the myoclonus occurring during natural sleep. Recently, etomidate has been reported to suppress adrenocortical function postoperatively (13).

Etomidate has also been shown to be effective and safe when used as part of a total intravenous anesthesia using a constant infusion of etomidate for maintenance of anesthesia with fentanyl for analgesia. This technique has been used successfully without incident in gynecological (14), general (15), and major vascular surgery (16). Constant infusion doses range from 0.018 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ (16) to 0.02 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ (17).

Because etomidate has also been reported to lower cerebral blood flow and metabolism (18) it has been considered advantageous for neurosurgical procedures. We report a neurosurgical case using a constant infusion of etomidate for hypnosis with supplemental boluses of fentanyl for analgesia that resulted in prolonged myoclonus on emergence.

Case Report

A 75-yr-old 88-kg male (ASA physical status II) with a 3-year history of right leg sciatica and poorly localized right pedal paresthesia was admitted for neurosurgical evaluation. He had no significant past medical history. Physical examination on admission was unremarkable, including a completely normal neurologic examination. The patient underwent an exploration of L4–5 with discectomy and an L4–5 laminectomy.

The patient received 50 mg of diphenhydramine intramuscularly 2 hr before surgery. Induction of anesthesia was achieved using etomidate 26 mg (0.3 $mg{\cdot}kg^{-1}$ and 0.25 mg fentanyl. After administration of 120 mg of succinylcholine (1.4 $mg{\cdot}kg^{-1}$) the trachea was sprayed with 4 ml 4% lidocaine and intubated with a 9-mm endotracheal tube. Pancuronium (8 mg) was given. Five minutes after the initial induction bolus of etomidate, an infusion of etomidate (500 mg in 500 ml 5% dextrose in half normal saline) was started using an IVAC drip counter at a rate of 102 $mg{\cdot}hr^{-1}$ (~ 0.02 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$) for maintenance of anesthesia with 50% nitrous oxide in O_2. Ventilation was controlled to maintain end-tidal CO_2 at 35–40 mm Hg as measured by a mass spectrometer. Blood pressure was monitored continuously through a catheter in the left radial artery; systolic arterial pressure was kept between 120–140 mm Hg. The ECG was also monitored continuously and a nasopharyngeal thermistor inserted. Fentanyl was administered intermittently when systolic pressure increased above 140 mm Hg or when heart rate increased as a reflection of increased sympathetic activity.

The etomidate infusion was turned off approximately 20 min before the end of the 4 hr operation. The patient received a total of 350 mg etomidate (26 mg bolus for induction plus 0.0184 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ for 200 min) and 0.475 mg fentanyl during the operation. The patient received 1100 ml of 5% dextrose in lactated Ringer's solution, 1 unit of fresh frozen plasma and 6 units of platelets. Paralysis from neuromuscular blockade was reversed at the end of the operation with 3 mg of neostigmine and 1.2 mg of atropine.

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Address correspondence to Dr. Newberg, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905.

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When the patient demonstrated spontaneous respirations and intact respiratory reflexes, he was extubated.

The patient was, however, unresponsive to verbal commands although gross movement was present in all four extremities. Upon arrival in the recovery room, 30 min after termination of the etomidate infusion, the patient remained unresponsive to command but began having purposeless twitches in the face and all four extremities, the latter soon progressing to myoclonic movements requiring four point restraints used for the patient's protection.

The blood glucose level was 110 mg/dl, arterial Po_2 and Pco_2 were 102 and 40 mm Hg, respectively, arterial pH was 7.38, HCO_3^- 23 mEq/L, Na^+ 137 mEq/L, K^+ 3.2 mEq/L, and hemoglobin 12.3 g%. His temperature was 36.5°C. The myoclonic movements continued, but after 1 hr, the patient exhibited some purposeful movement and could converse minimally but did not obey commands.

Seventy-five minutes after arrival in the recovery room the myoclonic movements began to decline in intensity and for the first time the patient could follow simple commands such as moving his toes and hands. The myoclonic activity ceased 2.5 hr after discontinuation of the etomidate infusion.

When interviewed 10 hr after discharge from the recovery room the patient had no recall of postoperative events. Physical examination, including a neurologic examination, was unremarkable.

Discussion

Studies that have used a constant infusion of etomidate for anesthesia all report easy arousability and minimal postoperative side effects. Rocke et al. (14) reported a waking time of 16.6 min (range 1–125 min) and time to patient communication of 30.4 min in patients after a mean duration of anesthesia of 87 min with a mean dose of 90.2 mg of etomidate and 0.375 mg of fentanyl. All patients had uneventful stays in the recovery room. Florence (16) reported a total dose of 200–546 mg etomidate (0.0182 $mg \cdot kg^{-1} \cdot min^{-1}$) and 1.5–3.0 mg fentanyl during major vascular surgery. Postoperatively these patients remained drowsy for several hours but were rousable. No other side effects were noted.

Our patient received 350 mg etomidate (0.018 $mg \cdot kg^{-1} \cdot min^{-1}$) and 0.475 mg fentanyl, which are within the ranges of etomidate and fentanyl used by Florence (16) and Fragen et al. (17). However he experienced myoclonus for a prolonged period during his emergence from etomidate anesthesia.

Myoclonus has only been reported to occur during induction of anesthesia with etomidate. In the awake state the involuntary movements of myoclonus, which are produced in the extrapyramidal motor system, are normally prevented by inhibition from the cortex. During anesthesia, etomidate is believed to suppress these inhibiting cortical influences, thereby allowing the myoclonus. This myoclonus can be suppressed by treatment with diazepam or fentanyl, the main sites of action of which are in subcortical structures including the extrapyramidal motor system (12).

The occurrence of myoclonus on emergence from etomidate anesthesia has not been reported previously. When etomidate is used only for the induction of anesthesia, it is assumed that rapid redistribution and enough metabolism of etomidate takes place before the end of the operation that anesthesia of the cortex by etomidate is no longer present so that any myoclonus can be inhibited by the cortex. When etomidate is administered as a continuous infusion, other drugs given concurrently may inhibit the extrapyramidal system to prevent myoclonus. If etomidate is the primary anesthetic, it is postulated that myoclonus could occur when awakening from anesthesia if the extrapyramidal system emerged more quickly than the cortex that inhibits it. The time sequence of myoclonus and arousal observed in our patient supports this premise. On termination of the etomidate infusion no myoclonus was observed, indicating anesthesia of both the extrapyramidal system and the cortex. With time the myoclonus appeared, indicating emergence of the extrapyramidal system but residual anesthesia of the cortex. When the patient was fully awake the myoclonus disappeared.

It is concluded that myoclonus as an effect of the use of a continuous etomidate infusion for anesthesia may have adverse consequences in neurosurgical patients in whom adequate postoperative neurological evaluation may be delayed or hindered by the presence of sustained myoclonus.

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Obstetrical Lumbar Epidural Anesthesia in Patients with Previous Posterior Spinal Fusion for Kyphoscoliosis

Gary Feldstein, MD and Sivam Ramanathan, MD

Lumbar epidural anesthesia (LEA) may be difficult theoretically in patients with previous extensive spinal surgery, not only because it may be technically difficult to accomplish, but also because the spread of local anesthetics might not be complete in the epidural space. Therefore, some anesthesiologists consider previous spinal surgery a relative contraindication to LEA. Recently, sporadic reports have appeared describing the use of LEA in patients with anatomic abnormalities of the spinal column (1). This report describes the use of LEA in three patients who have had extensive spinal surgery for idiopathic kyphoscoliosis.

Case 1

A 25-yr-old primigravida was referred to us by her obstetrician. The patient had posterior spinal fusion done from the T4 to L2 level with Harrington rod stabilization 12 years ago. Postoperative pulmonary function was within normal limits and the patient had no neurologic symptoms. The patient was 6 months pregnant and the obstetrician was contemplating a cesarean section because of pelvic deformity. The patient refused general anesthesia. She was prepared to have the cesarean section under local anesthesia, if LEA was not possible. At the time of consultation, we discussed with her the theoretical difficulties that might be encountered during administration of LEA to patients with previous spinal surgery. She agreed to a spinal anesthetic in the event that LEA was difficult to achieve.

On the day of surgery, the patient weighed 69 kg and was 150 cm tall. She was given one liter of Ringer's lactate solution intravenously. She was placed in the left lateral decubitus position, with the operating table horizontal. The incisional scar in her back extended approximately from the T3 level to the upper border of the L3. The L3–4 intervertebral space was easily palpable and the epidural space was identified without difficulty at the L3–4 space using a 17-gauge Hustead needle by loss of resistance technique. After a 3-ml test dose of 1.5% lidocaine with 1:200,000 epinephrine, 12 ml of the same local anesthetic solution was injected through the needle. A Portex epidural catheter was then threaded easily 3 cm into the space and an additional 4 ml of the anesthetic solution was given through the catheter. All sacral and lumbar, and the lower six thoracic dermatomes were anesthetic to pinprick in 15 min and surgery proceeded uneventfully. There were no postoperative complications.

Case 2

A 31-yr-old, 32-week pregnant primigravida was referred to us by her obstetrician for prenatal consultation. The patient had a posterior spinal fusion done from the T4 to L4 level (without a Harrington rod) for idiopathic kyphoscoliosis at the age of 16. She expressed a desire to have epidural analgesia during labor. We discussed with the patient the potential problems with epidural anesthesia as we had done with the first case. She went into labor when 38 weeks pregnant, at which time she weighed 70 kg and was 156 cm tall. A combination of 50 mg of meperidine and 25 mg of promethazine was administered intravenously twice during the course of labor without adequate pain relief. The patient was extremely anxious and agitated when the cervical dilation reached 8 cm. The patient was placed in the left lateral decubitus, with the bed horizontal and a 17-gauge Hustead needle was inserted into the epidural space with ease at the L4–5 interspace, using the loss of resistance technique. A Portex epidural catheter was inserted 3 cm into the space without difficulty. After a 3-ml test dose of 1.5% lidocaine with 1:200,000 epinephrine, 4 ml of the same local anesthetic solution was injected. A sensory level of T9 was achieved with a good relief of pain during labor. The analgesia lasted approximately 80 min. A second dose of 13 ml of the

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Address correspondence to Dr. Ramanathan, Department of Anesthesiology, New York University Medical Center, 550 First Avenue, New York, NY 10016.

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same anesthetic solution was then injected in the sitting position to facilitate a low forceps delivery. This dose anesthetized all the sacral and lumbar roots and the lower three thoracic roots. There were no postoperative complications.

Case 3

This 21-yr-old primigravida (150 cm tall and weighing 56 kg) was not evaluated in the prenatal period. She went into labor and, when her cervix was 4-cm dilated, requested epidural analgesia. She had had a spinal fusion from T2 to L2 for idiopathic kyphoscoliosis 6 years earlier. The patient was placed in the right lateral decubitus position, with the bed horizontal. The epidural space was easily identified at L3–4 space by loss of resistance technique using a 17-gauge Hustead needle. The epidural catheter was threaded 3 cm into the space without difficulty. Seven ml of 1.5% lidocaine with epinephrine 1:200,000 produced a T8 level of analgesia in approximately 5 min. She, however, required cesarean section because of fetal heart rate deceleration, for which 22 ml of 1.5% lidocaine with epinephrine was injected in divided doses to produce a sensory level of T4. The neonatal Apgar scores were 9 and 10 at 1 and 5 min after delivery, respectively. There were no postoperative complications.

Discussion

These case reports show that LEA can be both safe and effective for relief of pain during labor and for cesarean section anesthesia in patients who have had surgery for kyphoscoliosis. The incidence of scoliosis reported in routine screening of school children is 13.6% (2). Although spinal curvatures of less than 10 degrees are found equally in males and females, curvatures of greater than 20 degrees that require treatment are as much as seven times more frequent in females. Recent refinements in the surgical and anesthetic techniques have improved the safety of surgical correction of idiopathic scoliosis. Thus the obstetrical anesthesiologists may be presented more frequently with such patients in the future.

The objective of posterior spinal fusion is to create a bony fusion of the spinal curve (3). The upper end of the bone fusion extends to the nonrotated vertebra just above the rotated vertebra. All rotated vertebrae are included in the fusion, and the lower end of the fusion includes the first nonrotated vertebra that is parallel in all its axes to the first sacral vertebra. Virtually no fusions extend below L4. Harrington rods are usually inserted to produce internal stabilization of the fused mass. This is done by first inserting the upper hook of the rod in the facet joint of the uppermost vertebra to be fused while the lower hook is inserted under the lamina of the lowest vertebra to be fused. All joint facets between the vertebrae are then excised, the laminae and transverse processes are decorticated, and the spinous processes together with interspinous soft tissues are removed. The defects thus created in the facet area and the spinous processes are filled with autogenous bone plugs. The Harrington distraction rod is inserted on the concave side, and the compression assembly on the convex side of the curvature (3). The compression assembly is anchored by individual hooks at T5–12 vertebrae. The two lowermost hooks are inserted under the laminae. Fusions usually take seven to ten months for proper healing. A fusion is deemed solid when vertical trabeculae are evident throughout the fusion mass, best seen on supine detail oblique views (3).

Before a decision is made to administer epidural anesthesia in patients with previous surgery for kyphoscoliosis, one should consider the following potential problems: 5–10% of patients may have persistent back pain even after corrective back surgery (2) and regional anesthesia in such individuals with residual, persistent back pain could result in litigation; the corrective surgery may not relieve pulmonary dysfunction and epidural anesthesia may cause further impairment by affecting the intercostal muscles (4); insertion of the epidural needle through the midline or lateral approach in the fused area will not be possible because of the presence of both scar tissue and bony mass; no spinous processes will be felt in the fused area; because the scar due to surgical incision usually extends below the fused vertebra, the insertion of the needle into the interspace just below the lower end of the rod may be difficult, and finally; the ligamentum flavum may be accidentally injured either during surgical decortication of the laminae or insertion of the lower hooks of distraction and contraction rods and the resulting scar tissue may, by producing narrowing of the epidural space, interfere with the spread of local anesthetic solutions injected into the epidural space (5,6). For example, Schachner and Abram (7) described a case in which scarring from intervertebral disc disease prevented the spread of local anesthetic below the L5 level. They used a second epidural catheter at the L4–5 level to produce adequate analgesia.

None of our three patients had neurologic or pulmonary problems after surgery for kyphoscoliosis. All were aware of the potential problems with epidural anesthesia. Roentgenograms of the spine were available, which enabled us to accurately assess the lowest nonfused vertebra. In all three patients, we could feel a free intervertebral space below the lower end of the incisional scar. The insertion of the epidural needle and the threading of the catheter into the epidural space were easily accomplished. The onset of action, the spread, dose requirement, the highest sensory level, and the duration of action of the local anesthetic solutions were not different from what we have seen in normal patients in our institution. None developed postoperative complications.

Other authors have used epidural anesthesia in analagous situations. Crawford et al. (1), for example, described use of LEA in patients who had had a spinal laminectomy and vertebral fusion for kyphoscoliosis. Their report did not, however, specify the type or extent of surgery. Vaagenes and Fjaerestad (8) reported the use of LEA in a patient who had a meningocele removed in childhood from her lumbosacral spine. Carlson et al. (9) also used LEA without problems in an obstetrical patient with severe uncorrected idiopathic kyphoscoliosis, and Walpole (10) used LEA for labor and delivery in a patient who had a Meureig Williams plate inserted from the L1 to L4 vertebrae. However, to our knowledge, no one has reported the use of LEA in patients who have had extensive posterior spinal fusion. We used LEA safely and effectively in three patients who had had corrective surgery for idiopathic kyphoscoliosis.

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Subarachnoid Hemorrhage and Intraoperative Electrocardiographic Changes Simulating Myocardial Ischemia—Anesthesiologist's Dilemma

Satwant K. Samra, MD, and Donald A. Kroll, MD, PhD

Since 1947 when Byer et al. (1) first reported an association between cerebral hemorrhage and electrocardiographic (ECG) changes, many other reports describing a variety of electrocardiographic patterns including those of myocardial ischemia and infarction after an intracranial hemorrhage have been reported in the cardiologic and neurologic literature. However, we are not aware of reports of similar intraoperative changes occurring in patients having clipping of cerebral aneurysms. In this report we describe a case that presented a diagnostic dilemma after induction of anesthesia. This patient required three separate anesthetic managements over a period of four weeks and posed problems of diagnosis and management because of ECG changes suggestive of acute myocardial ischemia associated with subarachnoid hemorrhage. This case demonstrates the advantages and disadvantages of cancelling surgery versus proceeding with surgery.

Case Report

Our patient was a 76-yr-old woman who had been suffering from bifrontal headaches for approximately 3 months. On the day of admission, the headaches became more severe and she started vomiting. During transport by ambulance to a community hospital, she had an episode of ventricular tachycardia followed by ventricular fibrillation with spontaneous conversion to sinus rhythm, followed in turn by sinus rhythm with premature ventricular beats (PVBs) and then sinus tachycardia with a rate of 160 beats/min. Ventricular ectopy was treated with 100 mg lidocaine given intravenously. A brief episode of unconsciousness, urinary incontinence, and vomiting also occurred during transport to the hospital.

On arrival in the emergency room, the patient was conscious and complained of generalized malaise. She reported a two-year history of hypertension and a hiatal hernia associated with heartburn. Current medications included propranolol 15 mg twice a day for hypertension, and Donnatol and Anacin as needed for headaches.

On physical examination the patient was moderately obese (height 150 cm, weight 80.5 kg), her blood pressure ranged from 122/80 to 140/90 torr; pulse 84–92 beats/min; respiration 16–29 beats/min. The only abnormal findings were bibasilar rales and altered neurological status with drowsiness and confusion but no focal neurological deficit. Hematological studies were normal, as were serum electrolyte levels. The chest x-ray showed cardiomegaly and possible left lower lobe atelectasis but no infiltrates. The electrocardiograph (ECG), shown in Figure 1, was interpreted as possible anteroseptal myocardial infarction (MI) of indeterminate age.

A provisional diagnosis of subarachnoid hemorrhage (SAH) was made and a cerebral angiogram and CAT scan were done. The angiography revealed a 6 × 6 × 12 mm aneurysm of left internal carotid artery in its supraclinoid segment and moderate ventricular dilation, which was also confirmed by CAT scan. The patient was transferred to the neurosurgical intensive care unit. A right radial arterial catheter was inserted for blood pressure monitoring. She remained hemodynamically stable.

Thirty-six hours after admission, the patient complained of headache and was scheduled for craniotomy for aneurysm clipping. She was brought to the operating room where monitoring of ECG and arterial pressure was started. Blood pressure was 145/80 torr and heart rate 70 beats/min with normal sinus rhythm. The patient was sedated by intravenous injection of 5 mg diazepam and 100 μg fentanyl. Anesthesia was

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Address correspondence to Dr. Samra, Department of Anesthesiology, University of Michigan Hospitals, 1405 E. Ann Street, Ann Arbor, MI 48109.

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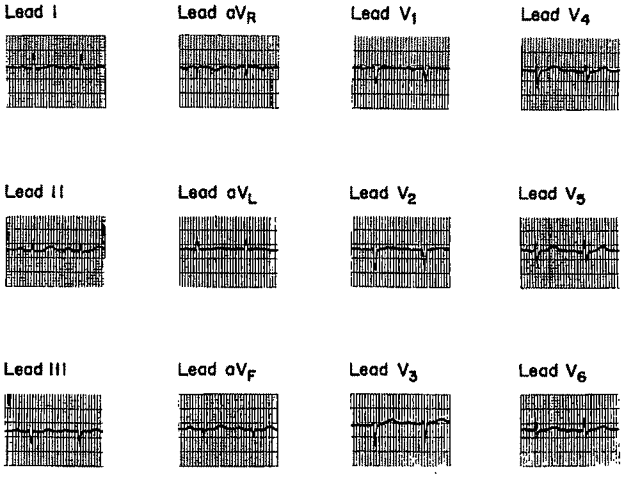

Figure 1. Preoperative electrocardiogram with possible old anterior septal infarction. No evidence of acute ischemia.

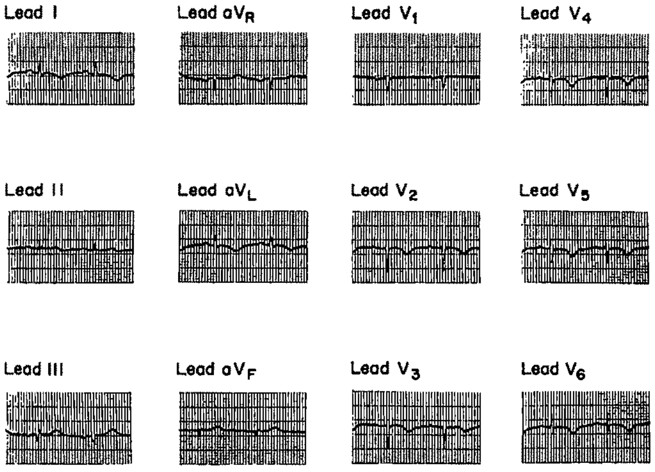

Figure 2. Intraoperative EKG showing symmetrical T-wave inversion in chest leads and ST segment elevation in leads II, III, and AVF.

induced with 100 mg thiamylal sodium and 7 mg pancuronium bromide. The trachea was intubated and mechanical ventilation with 50% nitrous oxide in oxygen was started. A lumbar subarachnoid catheter was inserted (for drainage of cerebrospinal fluid) and frankly blood stained cerebrospinal fluid was withdrawn. Thirty minutes after induction of anesthesia, but prior to surgical incision, a change in the ECG with ST segment and T-wave changes suggesting myocardial ischemia (Fig. 2) was noticed. The blood pressure was 90/60 torr with a heart rate of 60 beats/min. Fluid challenge increased blood pressure to 100/70 torr. Sublingual nitroglycerin was given with no change in ECG. Arterial blood-gas tensions at this time included a pH of 7.4, Pa_{CO_2} of 32.2 torr and a Pa_{O_2} of 242.7 torr, while being ventilated with 100% oxygen. After consultation with the neurosurgeons, it was decided not to proceed with surgery and the patient was taken to the recovery room. The cardiology consultant suggested that the ECG changes, although suggestive of acute ischemia, could possibly be due to subarachnoid bleeding. He recommended that a multiple gated acquisition (MUGA) scan, serial measurement of serum enzyme levels, and repeated ECGs be done to determine the extent of myocardial damage. After one hour, neuromuscular block was reversed. The patient was extubated and transferred to the intensive care unit (ICU). During the rest of the day, the patient's sensorium was waxing and waning. Later that evening, the MUGA scan revealed a left ventricular ejection fraction of 53% and apical, inferior wall and septal hypokinesis consistent with ischemic heart disease. The patient gave additional history of exertional dyspnea and questionable angina. The cerebral angiogram and CAT scan were repeated and showed the aneurysm as before with no vasospasm and unchanged or minimally increased size of intracranial ventricles. A ventriculostomy was performed to monitor intracranial pressure (ICP).

Over the next 48 hr, serum levels of lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and creatinine kinase MB (CK-MB) were measured every 6 hr. LDH and CPK levels remained within normal limits and none of the samples showed presence of CK-MB. ECG changes resolved over the next few days. The patient's sensorium was variably obtunded and there was a questionable seizure. The ICP remained low, and a pulmonary artery catheter was inserted. A volume expansion regimen for management of cerebral vasospasm as recommended in neurosurgical literature (25) was started to maintain a pulmonary capillary wedge pressure (PCWP) of 15–19 torr. Seventy-two hours after admission the patient became comatose and required tracheal intubation and mechanical ventilation. Another cerebral angiogram now showed severe vasospasm of the intracranial internal carotid circulation, and the patient remained comatose for five days before she started showing a slight improvement in her sensorium. After two weeks she was more alert and the endotracheal tube was removed. She continued to improve somewhat and was scheduled for a ventriculo-peritoneal shunt 21 days after the initial intracranial hemorrhage. By this time, the ECG showed upright T-waves in all chest leads.

On arrival in the operating room prior to induction of anesthesia, T-wave inversion in V5 was noted. It was decided to proceed with surgery. A pulmonary artery catheter was inserted and PCWP was found to be 10 torr and cardiac output 5.10 L/min. Anesthesia was induced with 250 μg fentanyl and 50% nitrous oxide in oxygen. The trachea was intubated after paralysis with pancuronium. She required two injections of 5 mg ephedrine for transient decreases in blood pressure prior to surgical incision. Anesthesia was maintained with 50% nitrous oxide in oxygen and 0.2–0.5% isoflurane. Because ST-depression and T-wave inversion persisted, a nitroglycerin infusion was continued throughout most of the surgery. T-wave inversion persisted throughout surgery despite administration of intravenous nitroglycerin. T-wave inversion resolved 24 hr postoperatively. Propranolol was used to control an increasing heart rate to 95 beats/min. Paralysis was reversed at the end of the procedure, but the patient was left intubated for the next 2 hr until full recovery of sensorium. Postoperatively, ECGs and enzymes were again taken for 48 hr to rule out myocardial infarction. Her neurological status started showing a slow improvement over the next week and ECG changes improved.

Four weeks after the initial SAH and one week after the ventriculo-peritoneal shunt the neurosurgeon decided that she would benefit from aneurysm clipping. Once again after establishing monitors of systemic and pulmonary arterial pressures and cardiac output, anesthesia was induced with 350 μg fentanyl, requiring supplementation by vasopressors twice before incision. The subsequent 9-hr course of anesthesia and surgery was unremarkable. No acute changes in ECG were noticed even when blood pressure was deliberately lowered to a mean arterial pressure of 50 torr for nearly 1 hr to facilitate clipping of the aneurysm. Postoperatively, she was mechanically ventilated overnight and extubated the next morning. By the next evening, the patient responded to verbal commands and was discharged from the ICU 3 days after surgery. Her sensorium slowly improved and she was discharged from the hospital 5 weeks after initial admission. She came for follow-up 6 months later without any focal neurological deficit but required further follow-up and treatment for dilantin toxicity.

Discussion

In 1947, Byer et al. (1) reported an association between cerebral hemorrhage and electrocardiographic changes consisting of prolongation of the Q–T interval and large T-waves. An electrocardiographic pattern simulating myocardial infarction was reported in association with subarachnoid hemorrhage in a woman with a normal heart at autopsy by Levine in 1953 (2). Although the most common electrocardiographic changes found in association with central nervous system lesions were first reported to be prominent T-waves, long Q–T intervals, and large U-waves (1,3,4), subsequent reports have confirmed that infarct patterns without myocardial damage (2,5–8), and subendocardial hemorrhage or myocardial infarctions (9–13) may also occur in association with subarachnoid hemorrhage. The association between cardiac arrhythmias, myocardial damage, and intracranial hemorrhage has been reviewed by Weidler (14).

The electrocardiographic changes occurring in our patient were remarkably similar to those reported by Cropp et al. (15). Their patient was a 55-yr-old woman with an intracranial hemorrhage. Because of the diagnosis of acute myocardial infarction by electrocardiographic criteria, surgery was not performed, although subsequent autopsy findings demonstrated a completely normal heart. We were likewise misled into delaying surgery by electrocardiographic changes resembling acute subendocardial infarction. Subsequent resolution of ECG changes and absence of serum CK-MB over the next 48 hr suggested that our patient did not have myocardial infarction. Although it is possible that a small subendocardial infarction may not always be associated with abnormal levels of the serum isoenzymes, measurement of serum CK-MB isoenzyme has nevertheless been recommended as the most useful test for myocardial necrosis (16). Subsequent clinical course in our patient is also suggestive of absence of an acute myocardial infarction. T-wave inversion was again seen prior to induction of anesthesia 2 weeks later, but this time we decided to ignore it and she tolerated the surgical procedure without cardiovascular complications. Four weeks after the initial episode, she also tolerated a 9-hr operation including 1 hr of induced hypotension, without cardiovascular complications.

Because patients with cerebrovascular disease often have risk factors for coronary artery disease and may have a history of myocardial infarction, noninvasive cardiac evaluation, or even cardiac catheterization, may not be helpful in distinguishing the cause of electrocardiographic changes suggesting acute myocardial ischemia or infarction. In some cases there is considerable risk of cerebral damage and further neurological deficit if surgery is delayed. Further confusing the diagnosis is the possibility that the SAH is causing myocardial damage (14,17–20), presumably due to a massive release of catecholamines (21,22). Cruickshank et al. (20) have shown a strong correlation between high urinary levels of catecholamines and T-wave inversion, the presence of Q-waves, and prolongated Q–Tc interval in patients suffering from SAH. In their study it was considered likely that high urinary levels of catecholamines arise from hypothalamic stimulation due to presence of blood in the lateral ventricles. Thus the anesthesiologist is confronted with three possible explanations for such electrocardiographic changes: acute myocardial infarction coincidental with subarachnoid hemorrhage; acute myocardial infarction caused by subarachnoid hemorrhage; and electrocardiographic changes without acute myocardial infarction. There are also three possible surgical considerations: surgery can be delayed without risk; surgery cannot be delayed without risk; and surgery is imperative for survival.

When surgery is considered imperative for survival, the operation should proceed with invasive hemodynamic monitoring and very careful assessment of the need for hypotensive techniques. When surgery can be delayed without risk, we recommend noninvasive cardiac studies and serial cardiac enzyme determinations in an attempt to rule out acute myocardial infarction prior to surgery. When there is a risk associated with delaying surgery, we believe that increased awareness by the anesthesiologists that the electrocardiographic changes may be unassociated with true myocardial infarction or that the hemorrhage may be, in fact, causing a myocardial infarction, will lead to improved risk–benefit analysis, prevent unnecessary delays in operative intervention, and favorably influence the choice of anesthetic technique. Hunt and Gore (23) have shown that administration of propranolol decreases the frequency of myocardial lesions in a rat model of SAH. Neil-Dwyer et al. (24) have studied the effect of administration of propranolol and phentolamine on the clinical course of SAH in a double-blind study and have shown that these drugs may have a cardioprotective effect. Our patient was receiving propranolol preoperatively for control of hypertension; we are not certain to what extent this might have been helpful.

In summary, this case illustrates that patients with subarachnoid hemorrhage can present with ECG changes suggestive of and indistinguishable from those due to acute myocardial ischemia and infarction. Postponement of surgery in this situation may not be in the best interest of the patient and may result in an increase in neurological deficit.

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Letters to the Editor

Anaphylaxis to Chymopapain after Antihistamine Pretreatment

To the Editor:

Bruno et al. have described a case of hypotension with a test dose of chymopapain (1). Although they did a superb job of treating the anaphylactic reaction once it was recognized, they did not use their invasive monitoring to recognize the impending anaphylactic reaction in advance by appropriate analysis of the early hypotension that occurred. One also wonders why an additional dose of chymopapain was administered after the reaction to the test dose. The purpose of pretreatment with both H_1 and H_2 receptor blockers is not to prevent an anaphylactic reaction but rather alter the dose–response curve to histamine. Histamine release appears to produce the initial hypotension associated with anaphylactic reactions (2). A decrease in mean arterial pressure from 94 to 70 mm Hg although "mild and slow" is quite significant and indicates substantial histamine release, especially in view of pretreatment. Furthermore, antihistamines and even corticosteroids may not prevent secondary mediator release after activation of mast cells and basophils to release other important secondary mediators such as leukotrienes and prostaglandins. Further hypotension ensuing approximately 25 min after the initial chymopapain dose suggests that the unstored synthesized mediators were in fact being released (3).

Early prompt recognition and aggressive therapy are crucial to treating potentially life-threatening reactions as observed in the case reported by Bruno et al. Anesthesiologists must realize the use of antihistamines may alter the initial hypotensive response during anaphylactic reactions. Therefore even subtle changes in arterial pressure must be treated.

Jerrold H. Levy, MD
Section of Anesthesiology
The Emory Clinic
1365 Clifton Road, NE
Atlanta, GA 30322

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Relating Knowledge and Clinical Competency Skills

To the Editor:

Results of the study by M. Sivarajan et al. (Objective evaluation of clinical performance and correlation with knowledge. Anesth Analg 1984;63:603–7), were doubtlessly not surprising to the authors or other faculty heavily involved in clinical education. The study concluded that no correlation existed between subject matter knowledge and related psychomotor skills.

To provide a different conceptual perspective on the significance of these results, a simple statistical manipulation (squaring the r value to determine the extent of shared variance) shows that less than 5% of the residents' skill performance could be explained or attributed to their theoretical knowledge. These findings have broad implications for clinical anesthesia education beyond the authors' inference that written and oral examinations may not be entirely appropriate measures of clinical competence.

The implications are twofold. First, the study results clearly illustrate that the proverbial cart has again preceded the horse. That is, most faculty tend to emphasize and reward first, successful performance of technical skills and secondarily, the demonstration of a solid cognitive theoretical base. This fact is evident in the magnitude of difference between performance and cognitive test scores. The significance of this observation lies in the supposition that most skills acquired in the absence of theory are more aptly described as habits, a type of behavior that requires little or no thought and consequently the potential for costly mistakes in patient care. To put a resident in the position of "cognitive catch-up" to clinical skills will likely result in clinical performance that either ignores, or at best lacks, consistent and rational application of knowledge to the clinical decision making process.

The second point is a natural extension of the first. The differences between knowledge and skill scores imply that clinical faculty may not be consistent in their instructional purpose, i.e., to facilitate the application of relevant knowledge to clinical problems. Most students of the profession have natural and independent abilities to acquire knowledge and perform a variety of psychomotor tasks, neither of which requires extensive professorial input. What they do not have is the facility at successfully bridging the gap between the two. The role of clinical faculty is to facilitate the intellectual bridging of knowledge and psychomotor performance. If residents are persuaded of the importance and relevance of a clinical concept, they will commensurately appreciate the importance of knowledge as a necessary requisite of conceptual justification.

Should this practice become the rule rather than the exception, I would expect future students of this sort to yield data where differences between knowledge and skill performances might be less incriminating.

Scot Foster, PhD, CRNA
Assistant Professor
University of Kansas
Kansas City, KS 66103

In Response:

The statement above that, "the study concluded that no correlation existed between subject matter knowledge and related psychomotor skills" is a misinterpretation. Our manuscript states that "we found no correlation between clinical performance and knowledge." In a study of different design, it may be possible, and I dare say likely, to find a correlation. For this, I suggest that a study comparing a group of anesthesia residents with a naive group, e.g., carpenters or college students, would find a strong positive correlation between knowledge and motor skills in the performance of spinal anesthesia, but little benefit would accrue to us from the study.

The more direct implications of our finding are that the objective evaluation of residents should be done not only in the cognitive area but also in the motor skill and attitudinal domains. I further think, that since we could not infer the performance from that observed in one domain to that expected in another, that our teaching and our evaluation should be in all three areas. I will not address Dr. Foster's remarks regarding the inadequacies of clinical teaching manifested by our results since these are predicated upon assumptions concerning the instruction that reflect his biases.

Elliott V. Miller, MD
Department of Anesthesia
Massachusetts General Hospital
Boston, Massachusetts 02114

Transillumination of the Trachea with Flexilum

To the Editor:

Transillumination of the trachea has been a valuable aid during difficult intubations (1,2). When a device with a lighted tip, such as a fiberoptic bronchoscope, is passed through the vocal cords, the trachea is transilluminated, and an endotracheal tube can be advanced into the trachea over the light to assure proper positioning of the tube. We would like to recommend an alternative to the fiberoptic bronchoscope, which often is not readily available during an emergency intubation.

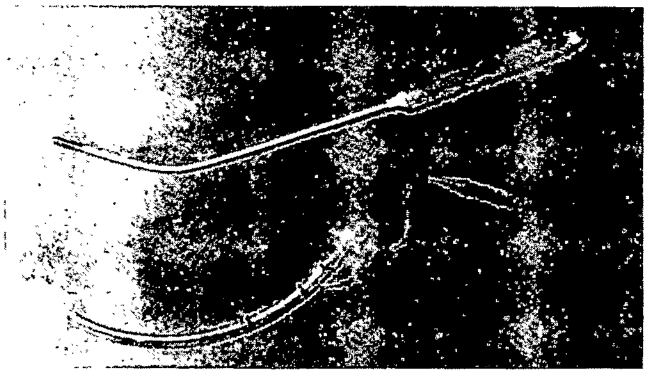

Figure 1. Flexilum with shortened endotracheal tube.

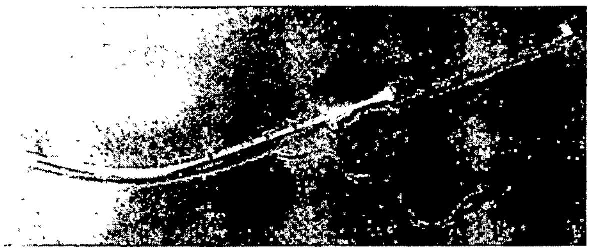

Figure 2. Illumination of endotracheal tube with flexilum.

The Flexilum (Concept, Inc., Clearwater, FL), which is used in orthopedics for intraarticular illumination, can serve as a transilluminator. Because it is a surgical light with the same diameter and flexibility of an endotracheal tube stylet, it can be used in place of one.

We have used the Flexilum as a stylet in 10 patients. Because of the 25-cm length of the Flexilum, we cut the endotracheal tubes to 26 cm. This allowed us to advance the light to within 1 cm of the tip of the tube and bend it as indicated in Figures 1 and 2. During laryngoscopy, we found it useful for an assistant to describe the location and intensity of the illumination on the surface of the neck. This facilitated two difficult intubations during which the vocal cords could not be seen. Transillumination provided a guide to the location of the tip of the endotracheal tube. When the transillumination was the brightest, as seen over the trachea, the endotracheal tube was advanced successfully into the trachea. In one instance, we inadvertently advanced the Flexilum into the esophagus, and no transillumination occurred.

One advantage of the Flexilum became evident to us when the laryngoscope light failed. The light of the Flexilum was sufficient to visualize the larynx, and enabled us to intubate the trachea.

The light weight (approximately 4 oz), portability, low cost ($18.00), and reusability (if cleaned properly) of the Flexilum should justify its widespread use during difficult intubations. Although refinements for anesthetic purposes would be welcome (e.g., increased length, smaller size for pediatric tubes), we nevertheless have found the Flexilum to be useful in anesthesiology.

Michael Hammer, MD
Brendan Garry, MD
Department of Anesthesiology
Boston University School of Medicine and
University Hospital
75 E. Newton St
Boston, MA 02118

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Unusual Complication of a Central Venous Catheter

To the Editor:

Recently, we encountered an unusual complication while using a multiorifice catheter, the Blitt Maxi Kit I, manufactured by Argon (Argon Medical Corporation, Athens, TX).

A 54-yr-old woman with a cervical spinal cord tumor was scheduled for cervical laminectomy and excision of tumor in the sitting position. After uneventful induction of anesthesia, the patient was positioned in the supine 15° head down position with the face rotated 30° to the left. The right side of the neck was cleansed and draped in sterile fashion and a Blitt Maxi Kit I was opened. Using a 22-gauge 4-cm needle, the right internal jugular vein was located easily. A 16-gauge 6-cm catheter was inserted in the jugular vein, parallel to the 22-gauge needle. After checking for good blood flow, a spring guide wire was advanced without difficulties. The 16-gauge catheter was removed, a small incision was made on the skin using a N°11 surgical blade, and a 20-cm long 16-gauge radiopaque polyurethane catheter was introduced over the guide wire without difficulties. The guide wire was removed. Blood flow back through the catheter was, however, unsatisfactory, and gentle manipulation did not improve it. The guide wire was reintroduced in the catheter without difficulties. An attempt was made to remove the catheter leaving the wire in place, but there was considerable resistance. A decision was made to remove the catheter and the wire together, which was accomplished without major problems (Fig. 1).

Examination of the catheter revealed that the J tip of the guide wire had exited through one of the lateral holes of the catheter and was locked in that position (Fig. 2).

It was decided to use a different central venous catheter, and cannulation of the right internal jugular was again performed without difficulty. The patient was subsequently placed in the sitting position and the surgical procedure performed uneventfully. The patient recovered from anesthesia and surgery without complications.

We tested several other kits in the laboratory and found that the guide wire exited through the lateral hole of a multiorifice catheter repeatedly. Each time that the plane of the curvature of the J tip in the guide wire was perpendicular to a lateral hole in the catheter, the guide wire would exit in that direction, as happened in our patient.

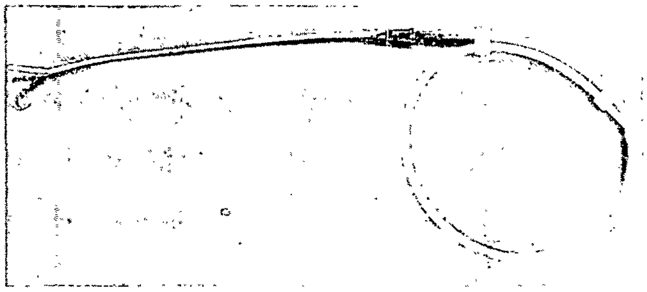

Figure 1. Central venous catheter removed from patient.

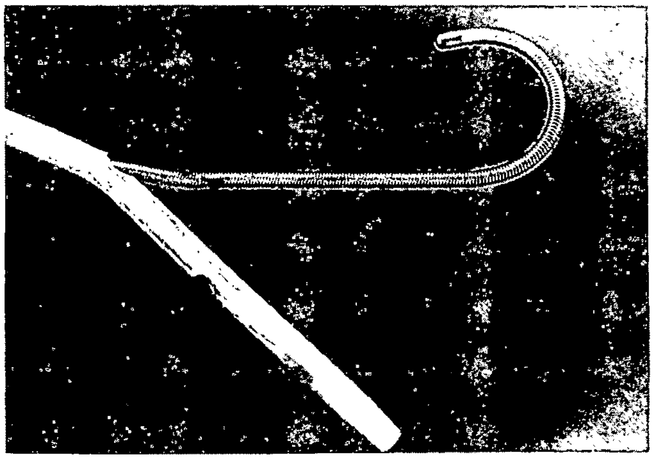

Figure 2. J tip of the guide wire exits through lateral hole.

We believe that the concept of a multiorifice central venous catheter is a valuable one, specially when inserted for procedures done in the sitting position. The problem reported here would not occur if the catheter were inserted and functioned without problems. However, if it becomes necessary to reinsert the guide wire, we strongly recommend using the straight end tip, to avoid the problem we encountered.

The manufacturing company has been informed of this problem.

Carlos U. Arancibia, MD
William D. Hawk, MD
University of Oklahoma Health Sciences Center
Department of Anesthesiology
PO Box 53188
Oklahoma City, OK 73152

Prolonged Anesthesia with Isoflurane

To the Editor:

Caplan and Long reported a case of a patient anesthetized with enflurane (26.6 MAC-hr) and nitrous oxide (29.7 MAC-hr) for two days for reimplantation of eight severed digits (1). The patient awakened 69 hr after completion of the procedure. In the postoperative period the patient developed fever, hypertension, thrombocytopenia, and neutropenia. I was recently involved in a similar anesthetic for reimplantation of two digits. Isoflurane (25 MAC-hr) was used for anesthetic maintenance with oxygen and air. During the course of the anesthetic a left supraclavicular brachial plexus block was twice performed with 0.5% bupivacaine using the first rib as landmark. The patient was alert, awake, and extubated 30 min after arrival in the recovery room. Postoperative course was benign.

The combination of regional anesthesia with a "light" general anesthetic is a common technique. Isoflurane appears to be an acceptable agent for this because of its low rate of biotransformation.

It is certain that both nitrous oxide and enflurane have inherent toxicities. Nitrous oxide, in vivo, causes bone marrow depression (2,3) and may cause a reversible myeloneuropathy (4). The metabolism of enflurane releases fluoride ion that may cause ADH-resistant diabetes insipidus and renal insufficiency. One can only speculate as to the cause for prolonged awakening for Caplan and Long's patient. Total dose (MAC-hr) of an anesthetic agent does affect time to MAC awake, as shown by Lowe and Ernst (5). However, calculations indicate a wake-up time of 1 hr, not 3 days, as in Caplan and Long's patient. Therefore, the burden then shifts to nitrous oxide. This gas is eliminated within a few minutes of cessation of its delivery, so is it possible that N_2O causes a temporary neuronal change that led to the prolonged emergence described by Caplan and Long?

James Pearson, MD
Department of Anesthesiology
The University of Alabama in Birmingham
619 19th Street South
Birmingham, AL 35294

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Safety for Anesthesiologists

To the Editor:

Occupational hazards associated with exposure to trace concentrations of anesthetic vapors are a major problem in underdeveloped and developing nations where scavenging systems are often not feasible for economic reasons. These hazards make recruiting people into anesthesiology difficult. They also contribute to low morale among those already in anesthesiology. These problems might be substantially ameliorated or even eliminated if we had the answers to questions that we cannot ourselves supply because of the circumstances under which we work. Perhaps those in other countries could provide, by their investigations, the answers. If they could, they would make a major contribution to anesthesiology in underdeveloped and developing nations.

The questions are the following:

1) Is there a safe limit to the quantity of anesthetics that can be inhaled, adsorbed, or otherwise taken up by anesthesiologists without causing harmful effects either directly in themselves or genetically in their offspring?
2) What is the upper limit of a "safe contact period," i.e., the maximum number of working hours per day and the maximum number of such working days at a stretch?
3) Would a "rest period" after the "safe contact period" reduce the risks?
4) If the answer to 3) is affirmative, then how long should the "rest period" be during which an anesthesiologist should not be allowed to work in an atmosphere where he or she may be exposed to the anesthetics?
5) What is the best way to communicate recommendations made for 1) above, to the various governments, and to direct every national society of anesthesiologists to ensure that these recommendations are followed for the safety of anesthesiologists and, thereby, of patients?

Gopi N. Kalla, MD
Department of Anesthesiology
College of Medical Sciences
University of Benin
Benin City, Nigeria

Book Review

Post-anaesthetic Recovery

By Roger Eltringham, Michael Durkin, Sue Andrews.
New York: Springer-Verlag, 1983, 151 pp.

The postanesthetic recovery period is an integral part of the overall anesthetic and surgical management of the patient. As in the periinduction and intraoperative times, the postanesthetic period may be marked by events ranging from a smooth uneventful recovery to a stormy emergence with major complications. Along with the evolution of the anesthesia practice, we have come a long way in the design and organization of the recovery room since its first description by Florence Nightingale in 1863 (1).

This book presents these issues in an orderly, sound, and practical fashion. The first chapter deals with the organization of the recovery room, its design, equipment, staffing, policies, etc. The second chapter describes the routine procedures on arrival of the patient in the recovery room and means of assessing the functional status of the body systems. The third chapter covers the postanesthetic complications and their management. Recovery from specialized surgical procedures with their complications and treatment is the topic of the fourth chapter. The final chapter discusses the preoperative conditions affecting recovery.

The book offers a sound and practical plan of action for the management of postanesthetic complications based on proper clinical evaluation with emphasis on the technique of differential diagnosis. Concise, well-written, and easy to comprehend, it is recommended to anesthesiologists, recovery room personnel, and all those involved in the postanesthetic care of patients.

Mahmood Tabatabai, MD, PhD
Department of Anesthesiology/CCM
University of Pittsburgh
VA Medical Center
Pittsburgh, PA 15240

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Pharmacokinetics of Anaesthesia. Cedric Prys-Roberts, Carl C. Hug JR. Massachusetts: Blackwell Scientific Publications, 1984, 358 pp.

A Practice of Anaesthesia. Wylie, Churchill-Davidson. Chicago: Year Book Medical Publishers, 1984, 1261 pp, $89.95.

The Neuromuscular Junction. Roger A. Brumback, Jeffery Gerst. New York: Futura Publishing Company, 1984, 354 pp, $39.00.

A Guide for Authors

Manuscripts should be sent to:

Nicholas M. Greene, MD
Editor in Chief
Anesthesia and Analgesia
Yale University School of Medicine
333 Cedar Street, New Haven, CT 06510

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Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766-71 and *Lancet* 1982;284:1766-70.

Use the checklist given below for preparation of manuscripts:

General

- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
- ☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
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- ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.
- ☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.
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- ☐ Define all abbreviations except those approved by the International System of Units.
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- ☐ Case reports, reviews, and editorials do not require the above sections.
- ☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.
- ☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.
- ☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.
- ☐ Do not use patients' names, initials, or hospital numbers.
- ☐ Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.

☐ Recommendations, when appropriate, may be included.

References

☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.

☐ Identify references in text, tables, and legends by arabic numerals (in parentheses, on line).

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus*.

☐ The titles of journals must be abbreviated according to the style used in *Index Medicus*.

☐ Try to avoid using abstracts as references; "unpublished observations" and "personal communications" may not be used as references although references to written, not verbal, communications may be inserted (in parentheses) in the text. Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses). Authors citing as references articles from their own group that are in press and that have a bearing on the paper submitted should enclose 3 copies of an abstract of such in press materials.

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Journals:

1. *Standard Journal Articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
   You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980;79:311–4.
2. *Corporate Author*
   The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977;2: 242–4.
3. *No Author Given*
   Anonymous. Coffee drinking and cancer of the pancreas (Editorial). Br Med J 1981;283:628.
4. *Journal Supplement*
   Mastri AR. Neuropathy of diabetic neurogenic bladder. Ann Intern Med 1980;92(2 Pt 2):316–8.

   Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan (Abstract). Blood 1979;54(suppl 1):26a.
5. *Journal Paginated by Issue*
   Seaman WB. The case of the pancreatic pseudocyst. Hosp Pract 1981;16(Sep):24–5.

Books and Other Monographs:

6. *Personal Author(s)*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
7. *Editor, Compiler, Chairman as Author*
   Dausset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12–8.
8. *Chapter in a Book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.
9. *Published Proceedings Paper*
   DuPont B. Bone marrow transplantation in severe combined immunodeficiency with an unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974:44–6.
10. *Monograph in a Series*
    Hunninghake GW, Gadek JE, Szapiel SV, et al. The human alveolar macrophage. In: Harris CC, ed. Cultured human cells and tissues in biomedical research. New York: Academic Press, 1980:54–6. (Stoner GD, ed. Methods and perspectives in cell biology; vol. 1).
11. *Agency Publication*
    Ranofsky AL. Surgical operations in short-stay hospitals: United States—1975. Hyattsville, Maryland: National Center for Health Statistics, 1978; DHEW publication no. (PHS) 78–1785. (Vital and health statistics; series 13; no. 34).
12. *Dissertation or Thesis*
    Cairns RB. Infrared spectroscopic studies of solid oxygen (Dissertation). Berkeley, California: University of California, 1965. 156 pp.

Tables

☐ Type each table double spaced on a separate sheet. Do not submit tables as photographs.

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☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

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DESCRIPTION

Each ml. contains:
Fentanyl .... 50 mcg. (0.05 mg.) as the citrate
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS

SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS

AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safetv for the infant in obstetrics has not been established.

PRECAUTIONS

The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION

50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.
II. *Adjunct to General Anesthesia*—See Dosage Range Chart
III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.
IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE* injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE* injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE* injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE* injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE* injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE

Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

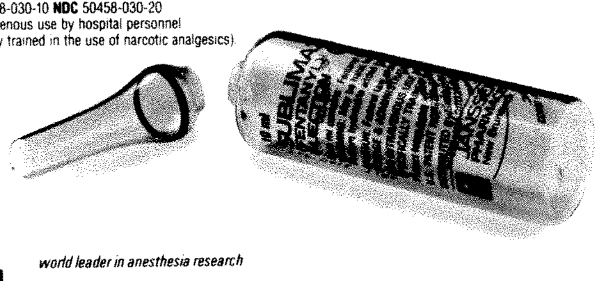
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED

2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980 Revised June, 1980, Jan. 1981, March 1983
U.S. Patent No. 3,164,600



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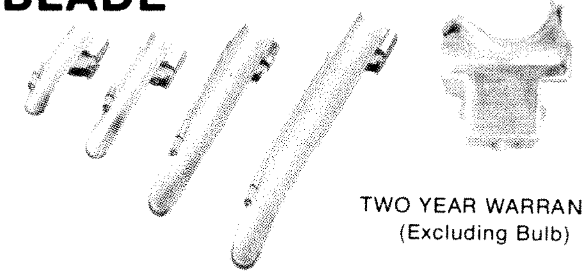

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NITROUS OXIDE/N_2O

Editor: **Edmond I. Eger II, M.D.,** Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

Nitrous Oxide/N_2O is a complete resource on the subject. It describes what is known about nitrous oxide – applications and contraindications – and debates its continued clinical use. The current clinical applications of N_2O are reviewed by means of:

- thorough discussion of N_2O pharmacology and distribution
- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. ***Nitrous Oxide/N_2O*** is a controversial work that everyone using the drug will want to read.

Contents. Preface. Contributors. A History of Nitrous Oxide. Physics, Chemistry, and Manufacture of Nitrous Oxide. Nitrous Oxide Analgesia. MAC. Nitrous Oxide Delivery Systems. Pharmacokinetics. Respiratory Effects of Nitrous Oxide. Cardiovascular Effects of Nitrous Oxide. Central Nervous System Effects of Nitrous Oxide. Neuromuscular Effects of Nitrous Oxide. Nitrous Oxide in Obstetrics. Metabolism of Nitrous Oxide. Nitrous Oxide Inactivates Methionine Synthetase. Mutagenicity, Carcinogenicity, and Teratogenicity of Nitrous Oxide. Nitrous Oxide Abuse. Toxicity of Nitrous Oxide. The Use of Nitrous Oxide by Dentists. Nitrous Oxide in Veterinary Practice and Animal Research. Controlling Occupational Exposure to Nitrous Oxide. Should We Not Use Nitrous Oxide. We Should Continue to Use Nitrous Oxide. Epilogue. Index.

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Brief Summary of Prescribing Information

INDICATIONS AND USAGE NARCAN is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and the narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected acute opioid overdosage.

CONTRAINDICATIONS NARCAN is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs.

PRECAUTIONS In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity and mutagenicity studies have not been performed with NARCAN. Reproductive studies in mice and rats demonstrated no impairment of fertility.

Use in Pregnancy: Pregnancy Category B: Reproduction studies performed in mice and rats at doses up to 1,000 times the human dose, revealed no evidence of impaired fertility or harm to the fetus due to NARCAN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

ADVERSE REACTIONS Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of NARCAN may result in significant reversal of analgesia, and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of NARCAN postoperatively (see PRECAUTIONS & USAGE IN ADULTS—POSTOPERATIVE NARCOTIC DEPRESSION). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

OVERDOSAGE There is no clinical experience with NARCAN overdosage in humans.

In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injection: no toxic effects were seen at 10 mg/kg/day for 3 weeks.

DOSAGE AND ADMINISTRATION NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN the patient should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of NARCAN in 500 ml of either solution provides a concentration of 0.004 mg/ml. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of narcotic induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one or two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Narcotic Depression Follow the recommendations and cautions under ADULT POSTOPERATIVE DEPRESSION. For the initial reversal of respiratory depression NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two to three minute intervals to the desired degree of reversal.

USAGE IN NEONATES Narcotic-Induced Depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M., or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

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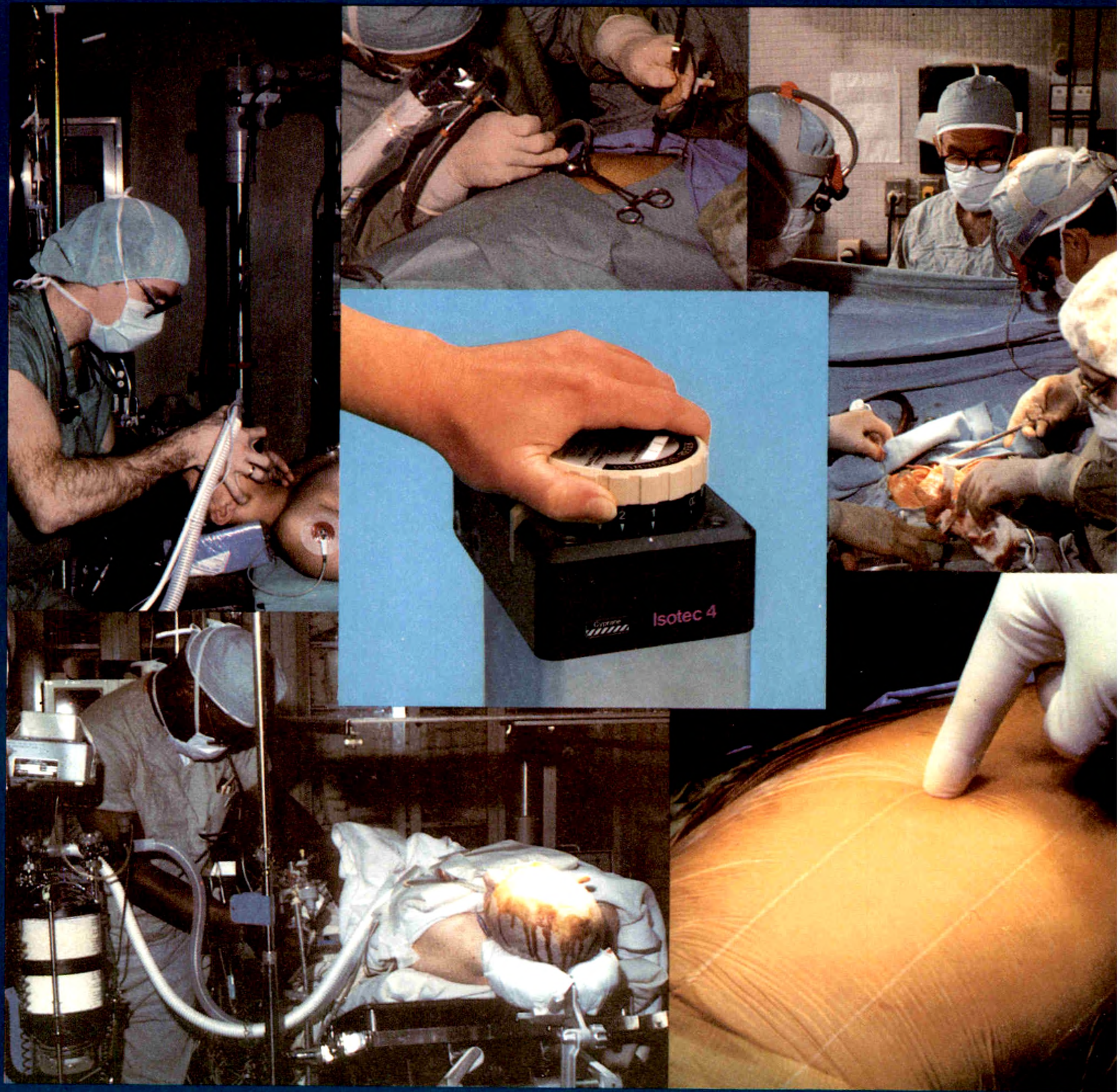

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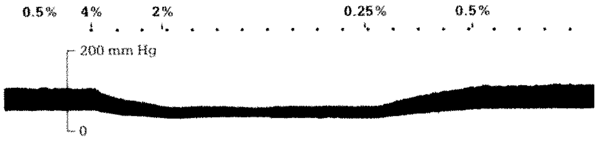
A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Plood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

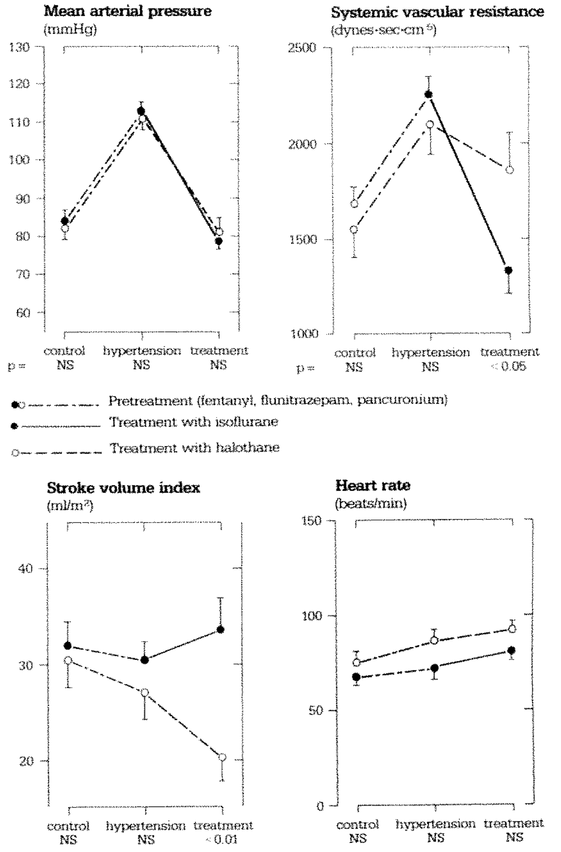
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surge (Adapted from Hess et al[3]).



Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)

Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8] *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

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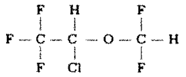
DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$F-\underset{F}{\overset{F}{C}}-\underset{Cl}{\overset{H}{C}}-O-\underset{F}{\overset{F}{C}}-H$$

Some physical constants are:

Molecular weight		184.5
Boiling point 760 mm Hg.		48.5 °C (Uncorr.)
Refractive index n_D^{20}		1.2990—1.3005
Specific gravity 25°/25 °C		1.496
Vapor pressure in mm Hg.**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = {}^\circ C + 273.16 \text{ (Kelvin)}$$

Partition coefficients @ 37 °C	
Water/gas	0.61
Blood/gas/gas	1.43
Oil/gas	90.8
Partition coefficients @ 25 °C—rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9 %
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23 °C	None
Lower limit of flammability in oxygen or nitorus oxide at 900 joules/sec and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anaesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

Age	100 % Oxygen	70 % N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administerd epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17 % of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known senitivity to FORANE (isoflurane) or other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing enivronment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and M.A.C. (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See Clinical Pharmacology.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at $\frac{1}{2}$, $\frac{1}{8}$, and $\frac{1}{32}$ M.A.C. for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting, and ileus have been observed in the postoperative period

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\%\ \text{isoflurane} = \frac{100\, P_V F_V}{F_T(P_A - P_V)}$$

where P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (ml)
F_T = Total gas flow (ml)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbituate. Inspired concentrations of 1.5 to 3 % isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia my be sustained with a 1.0-2.5 % concentration when nitrous oxide is used concomitantly. An additional 0.5 % to 1.0 % may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

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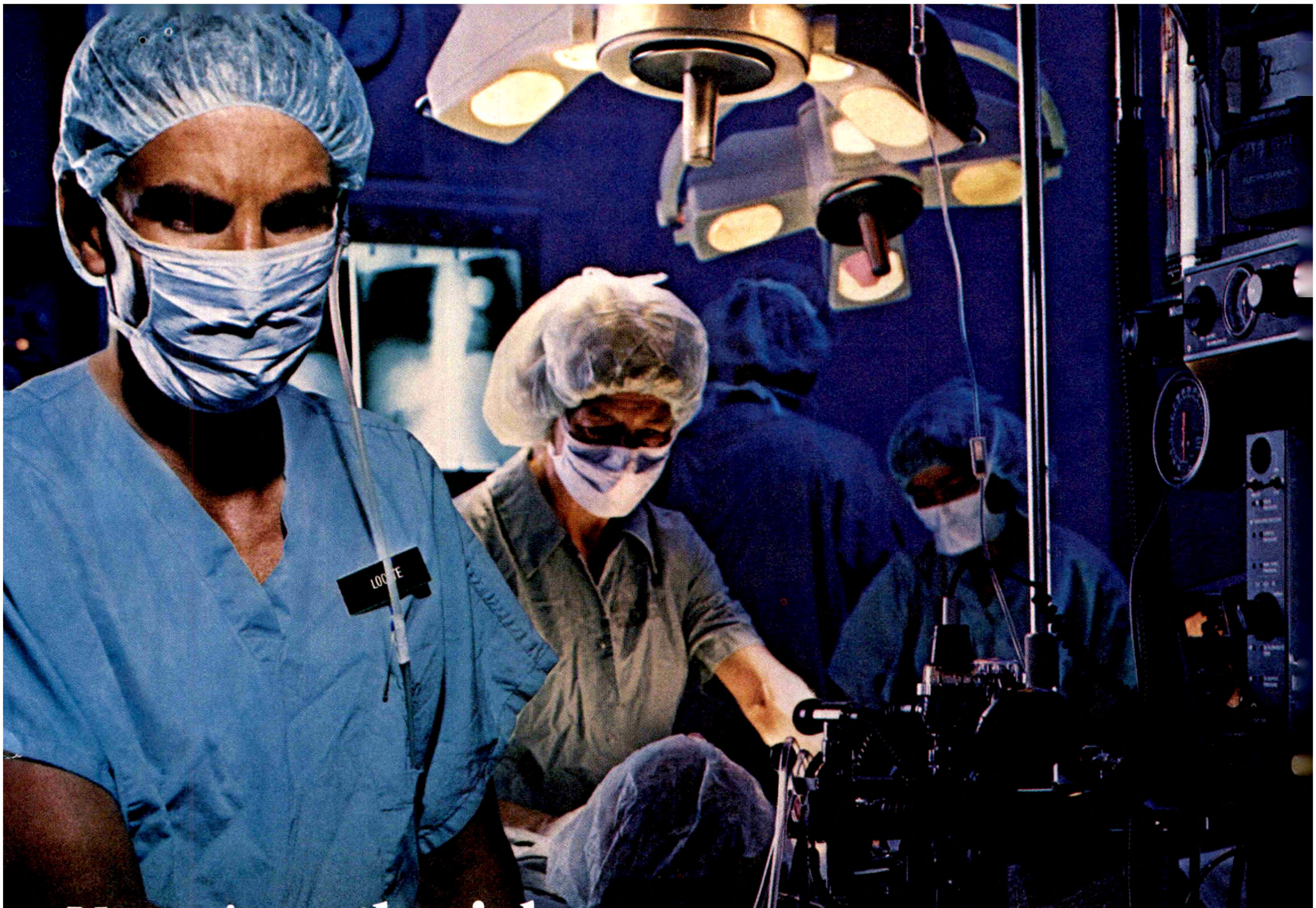

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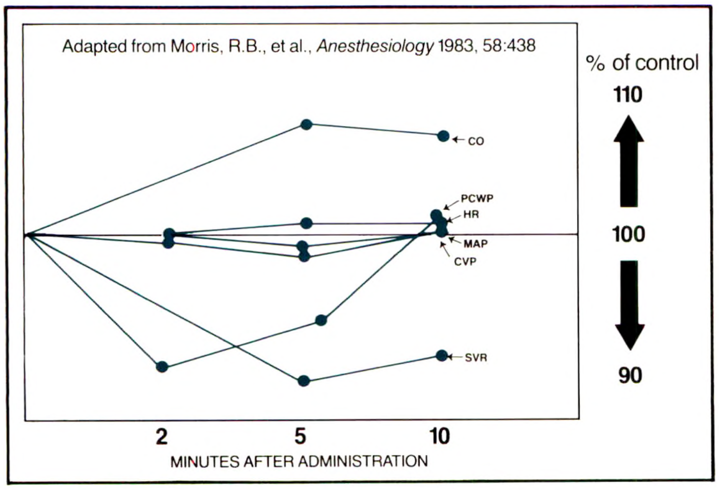
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The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate[5]

			Percent of Control		
Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
tubocurarine	0.5	1	318	78	116
metocurine	0.5	2	212	79	119
atracurium	0.6	3	192	80	108
vecuronium	0.1	1.7	117	100	99
vecuronium	0.2	3.5	87	99	102

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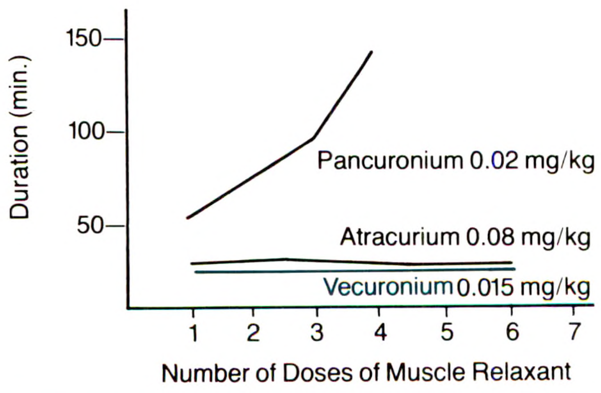
The Neuromuscular Effects of Maintenance Doses of Vecuronium, Atracurium and Pancuronium[6,7]



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pancuronium	3:1	metocurine	2:1
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*cannot be calculated since it does not cause any CV or histamine related effects

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A Comparison of Surgical Muscle Relaxants vs. The Ideal[4]
(" + " signifies proximity to the ideal)

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Onset of Action	–	–	–	+	–
Histamine Release	+	–	+	+	–
Cardiovascular Side Effects	+	+ / –	–	–	–
Duration of Action	+	+	–	+	–
Cumulative Effects	+	+	–	–	–
Rate of Recovery	+	+	–	+	–
Reversibility	+	+	+	–	+
Potency	+	+	+	–	–
Non-depolarizing	+	+	+	–	+
Metabolite Activity	+	+*	+	+	+

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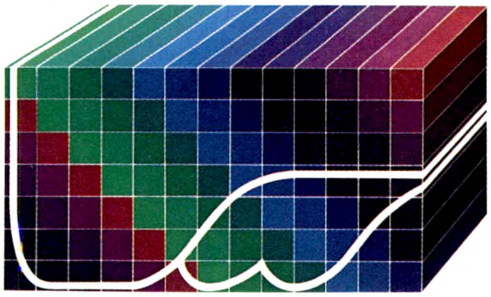

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Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.[4]

Organon

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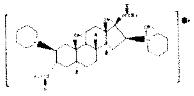
NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON* (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis (acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methyl-, bromide. The structural formula is.



Norcuron* is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron* (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron* is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron* is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron* dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron* is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron* is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron* (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron*, the administration of Norcuron* should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron* has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron* has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron* neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron* (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron* induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron* is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron* varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron* has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron* (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron* in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron* within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron*. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron* in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron* during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron* (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron* is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron* (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron* should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron* metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING

way and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron* (vecuronium bromide for injection).

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia.

Norcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* and its duration of action. If succinylcholine is used before Norcuron*, the administration of Norcuron* should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron* (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron*; therefore these drugs and Norcuron* may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron* will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron* may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron* (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron*. It is also not known whether Norcuron* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron* should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron* (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron* was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron* as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron* is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron* overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron* (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron* as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol* (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron*. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron* (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron* by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron* is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron* (vecuronium bromide for injection) is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron*. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron* to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron* are recommended; after the initial Norcuron* injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron* lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron* is compatible in solution with

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringers

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10

STORAGE: PROTECT FROM LIGHT Store at 15°-30°C (59°-86°F)

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

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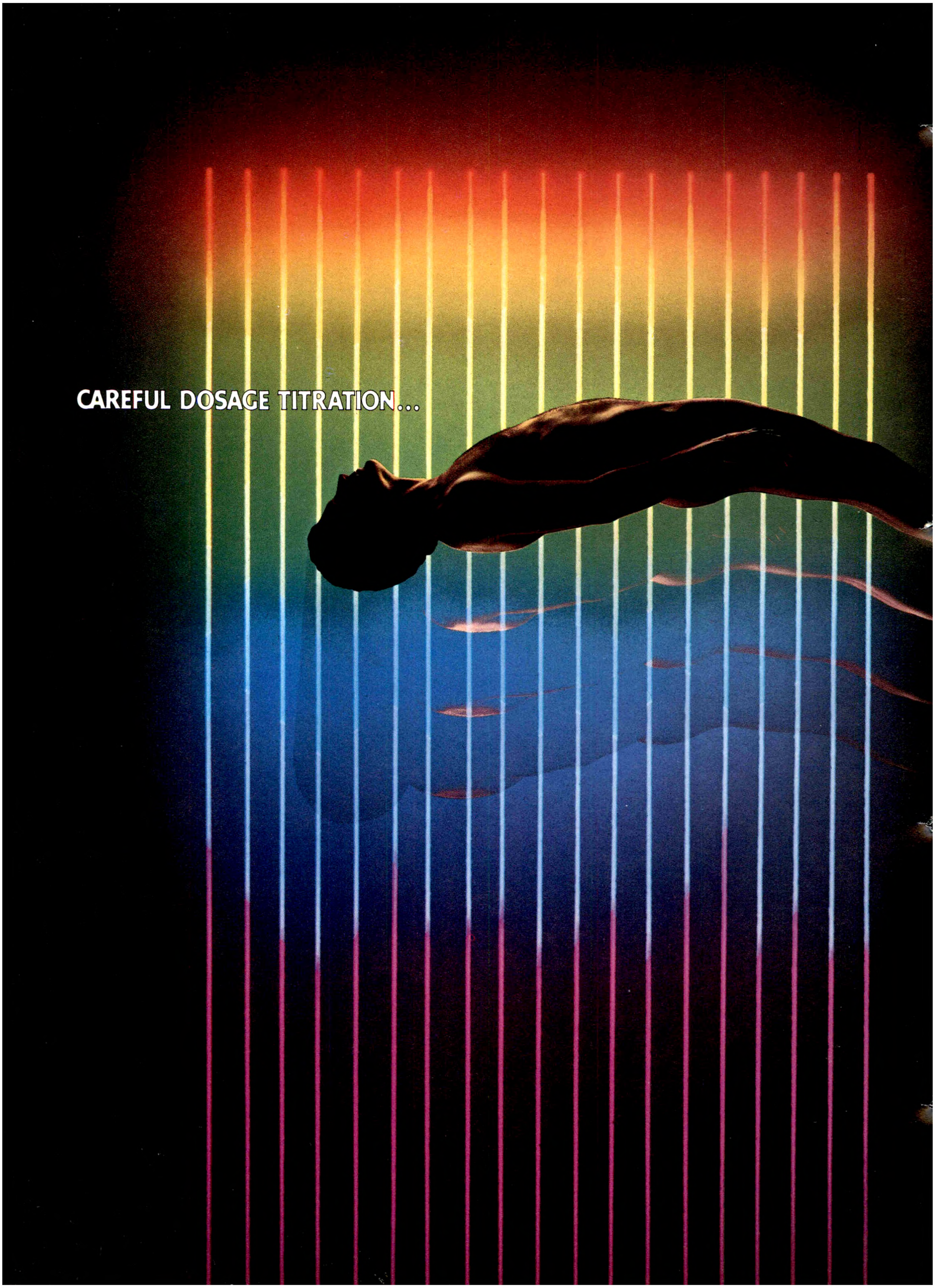
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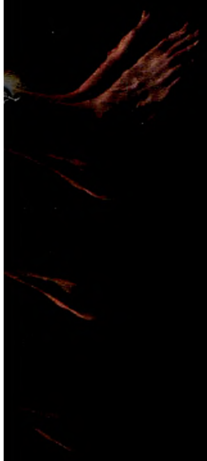

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10-ml vial

Following narcotic-supplemented anesthesia, a gradual upward titration with NARCAN® (naloxone HCl) helps achieve the desired degree of narcotic reversal, allowing adequate ventilation and alertness without significant pain or discomfort. By restoring the patient's protective reflexes, NARCAN reduces the risk of postanesthetic complications. Patients can often leave recovery sooner and be returned to their rooms—a practical advantage both for the patient's concerned family or friends and for the busy medical staff.

For initial reversal of postoperative respiratory depression in adults, NARCAN (0.4 mg/ml) should be injected in increments of 0.1 to 0.2 mg (1/4 to 1/2 ml) intravenously at two- to three-minute intervals. The duration of action of some narcotics exceeds that of NARCAN. It is important, therefore, to monitor patients carefully and give repeated doses of NARCAN as needed.

NARCAN (0.4 mg/ml) is available in 1-ml ampuls and 10-ml vials. Also available, NARCAN® NEONATAL INJECTION (naloxone hydrochloride). Each 2-ml ampul contains 0.02 mg/ml.

For brief summary of prescribing information, see next page.
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NARCAN®
naloxone HCl

NARCAN® INJECTION
NARCAN® NEONATAL INJECTION (naloxone hydrochloride)
Narcotic Antagonist
Brief Summary of Prescribing Information

INDICATIONS AND USAGE NARCAN is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and the narcotic-antagonist analgesics, nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected acute opioid overdosage.

CONTRAINDICATIONS NARCAN is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs.

PRECAUTIONS In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity and mutagenicity studies have not been performed with NARCAN. Reproductive studies in mice and rats demonstrated no impairment of fertility.

Use in Pregnancy: Pregnancy Category B. Reproduction studies performed in mice and rats at doses up to 1,000 times the human dose, revealed no evidence of impaired fertility or harm to the fetus due to NARCAN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

ADVERSE REACTIONS Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of NARCAN may result in significant reversal of analgesia, and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of NARCAN postoperatively (see PRECAUTIONS & USAGE IN ADULTS—POSTOPERATIVE NARCOTIC DEPRESSION). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

OVERDOSAGE There is no clinical experience with NARCAN overdosage in humans.

In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injection; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

DOSAGE AND ADMINISTRATION NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN the patient should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of NARCAN in 500 ml of either solution provides a concentration of 0.004 mg/ml. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of narcotic induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one or two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Narcotic Depression Follow the recommendations and cautions under ADULT POSTOPERATIVE DEPRESSION. For the initial reversal of respiratory depression NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two to three minute intervals to the desired degree of reversal.

USAGE IN NEONATES Narcotic-Induced Depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M., or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

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0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available as:

2 ml ampuls in boxes of 10	NDC 0590-0367-10

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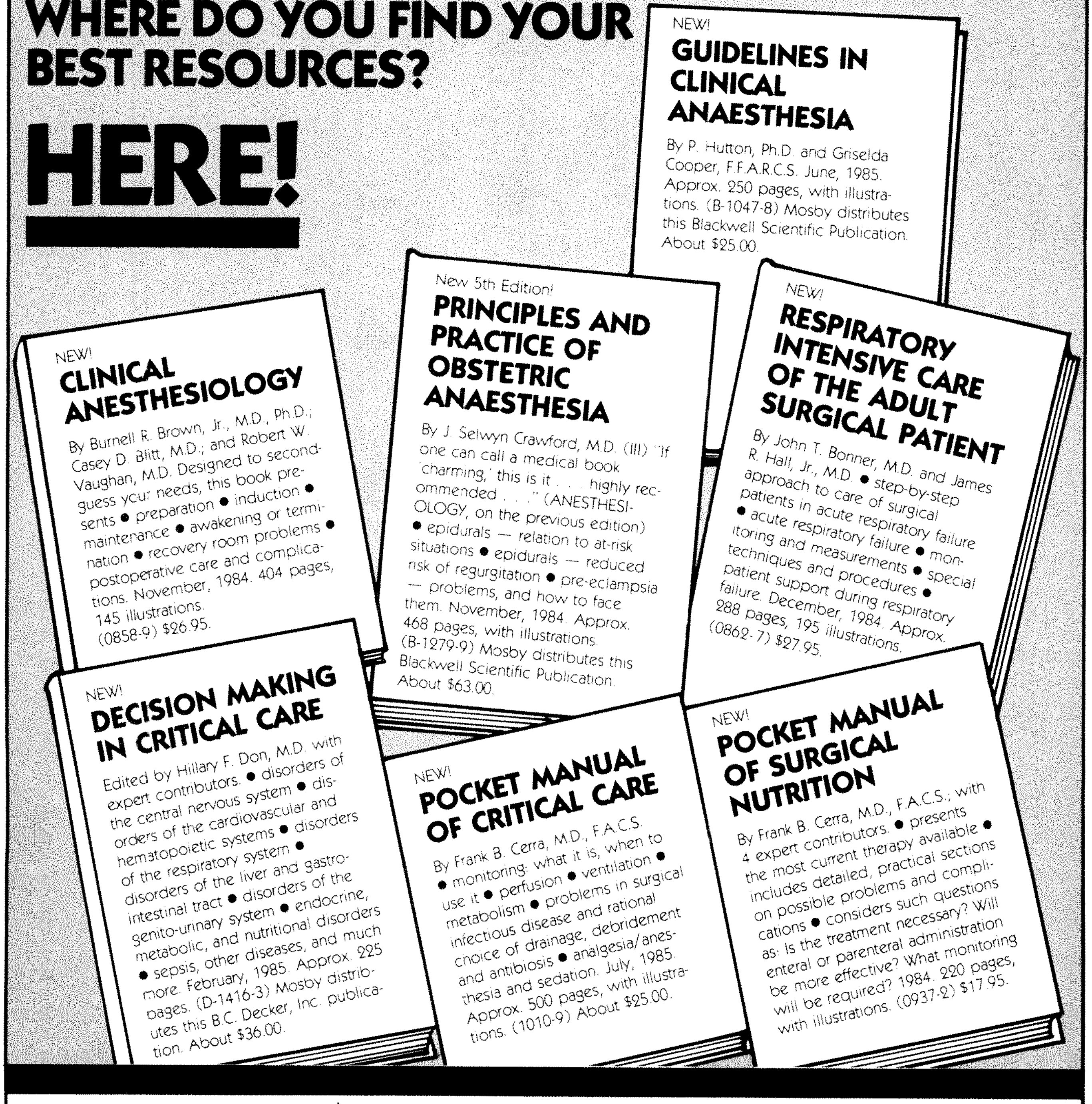

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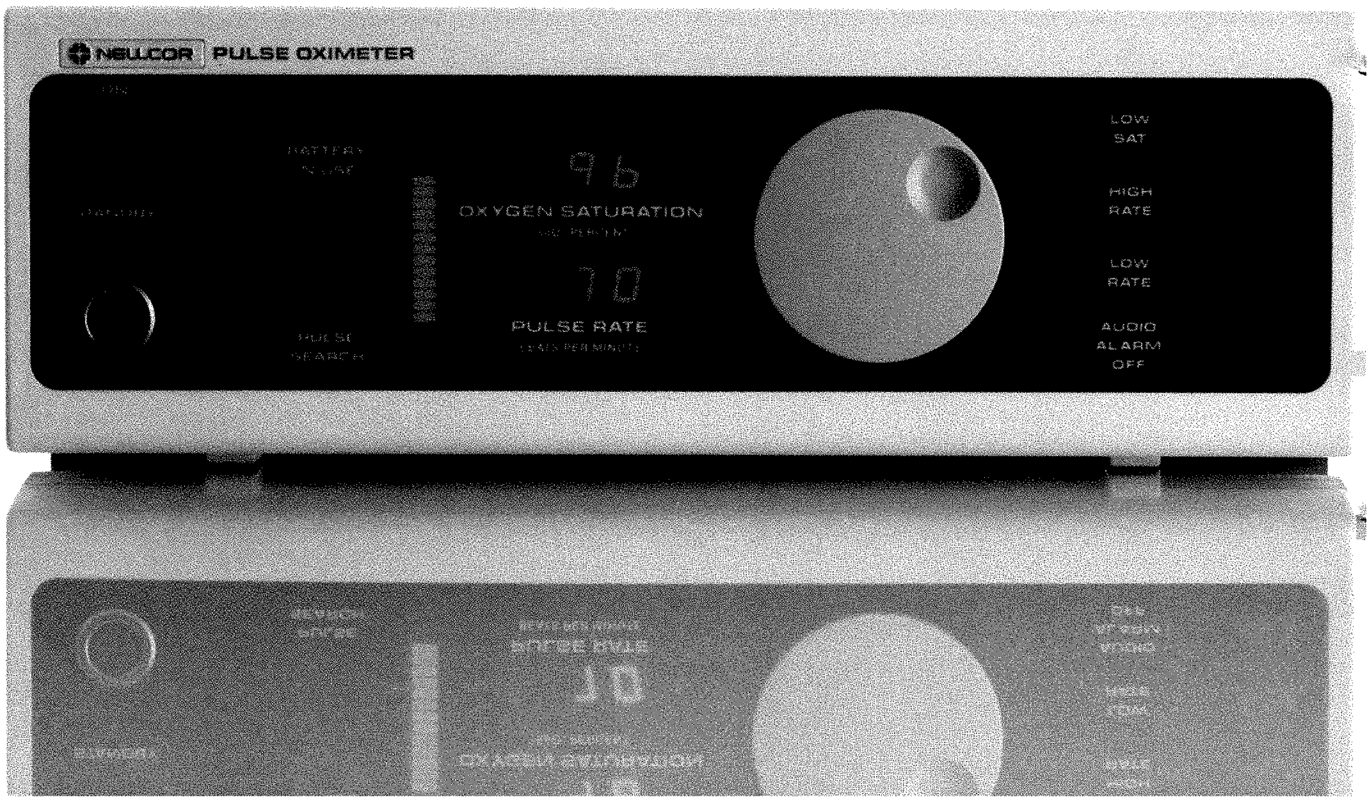

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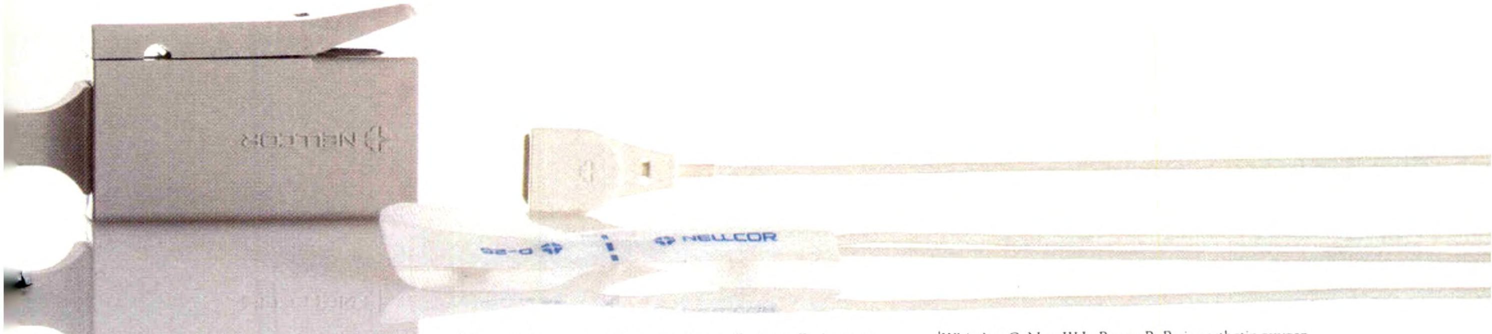

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[1] Flynn M: Hypoxemia Detection During Pediatric Endoscopy. Presented at The American Academy of Pediatrics, 1983, pp 1-2.

[2] Davis DA: An Analysis of Anesthetic Mishaps from Medical Liability Claims, in Pierce EC Jr, Cooper JB (eds): *Analysis of Anesthetic Mishaps*. International Anesthesiology Clinics, Boston, Little, Brown and Company, 1984, Vol 22, No 2, pp 31-42.

[3] Rubsamen DS (ed): Professional Liability Newsletter, 1984, Vol 15, No 6.

[4] Whitcher C, New W Jr, Bacon B: Perianesthetic oxygen saturation vs. skill of the anesthetist. Anesthesiology 57: 1982. Suppl to abstract for American Society of Anesthesiologists, October 18, 1982.

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*Coakley C, Levy ML, Epstein B: *Fentanyl in short surgical procedures: Dilatation and curettage.* A medical film...available from your Janssen Representative.

The respiratory depressant effect of SUBLIMAZE may be longer than the analgesic effect.
Please see brief summary of Prescribing Information on next page.

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Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

DESCRIPTION

Each ml. contains:
Fentanyl .... 50 mcg. (0.05 mg.) as the citrate
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS

SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS

AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS

The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION

50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.
II. *Adjunct to General Anesthesia*—See Dosage Range Chart
III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.
IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE® injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE® injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE® injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE® injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE® injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE

Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED

2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. Jan. 1981, March 1983
U.S. Patent No. 3, 164 600

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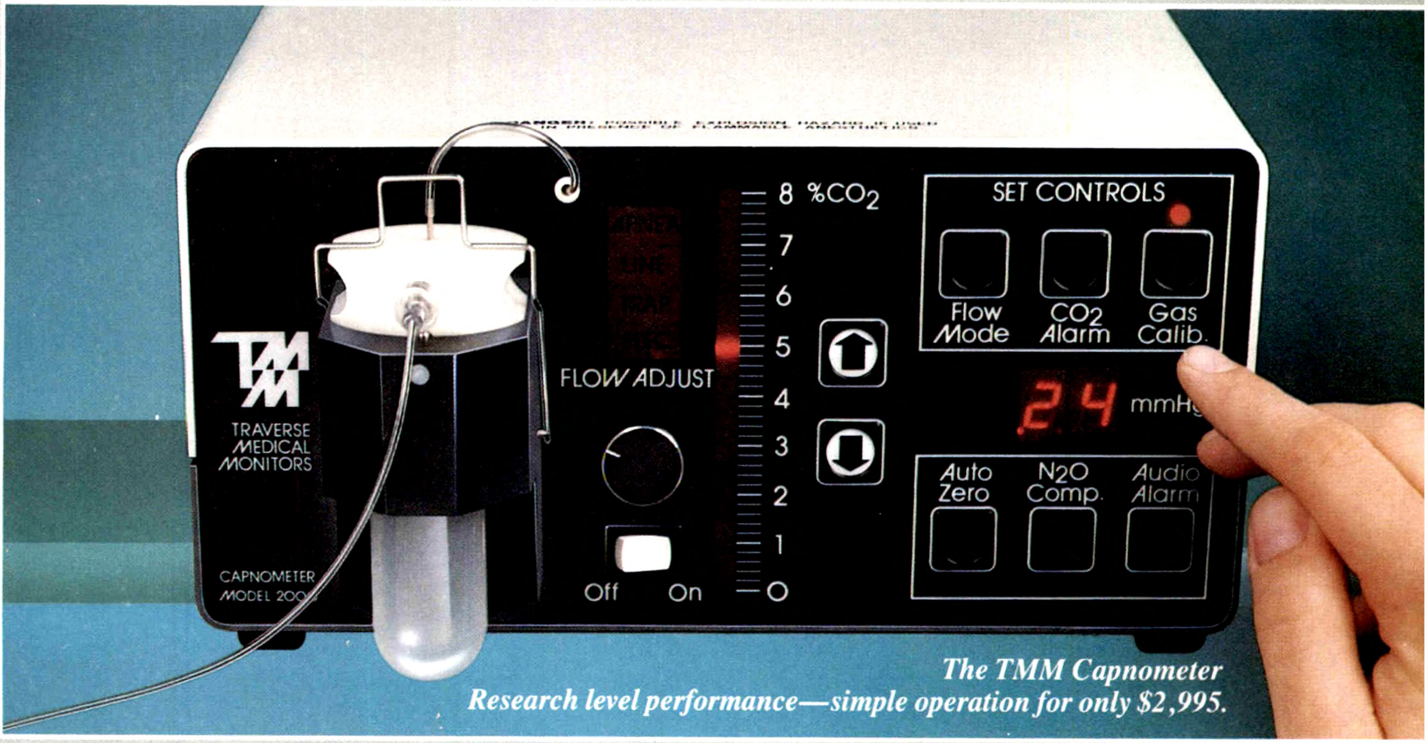
JPI-485

Forget your old ideas about capnometers.



The TMM Capnometer
Research level performance—simple operation for only $2,995.

Ours is easy to use.

The TMM Capnometer is simple to operate. Just connect the Capnometer to the patient or the ventilator circuit, and turn it on. To set parameters, as illustrated by the gas calibration procedure above, you simply press tactile response buttons.

Thanks to a powerful microprocessor, the TMM Capnometer monitors itself so you can give more attention to your patient. The Capnometer alerts you when a trend has been determined that deviates from parameters you have established.

All user selected operating parameters are retained in memory. Automatic baseline updates provide long term unattended operation.

Data display is clear, bright, and continuous. A linearized signal output enables you to observe end-tidal waveforms.

An advanced Fluids Separator* on the TMM Capnometer continuously clears the gas stream of fluids.

A reliable infrared analyzer counts CO_2 molecules in under 100 msec at a flow rate of 260 ml/minute—a rate comparable to dedicated mass spectrometers and faster than multiplexed units.

The TMM Capnometer is backed by a comprehensive user support and service program. And it costs only $2,995.

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*patent pending

Soothing news for busy anesthesiologists

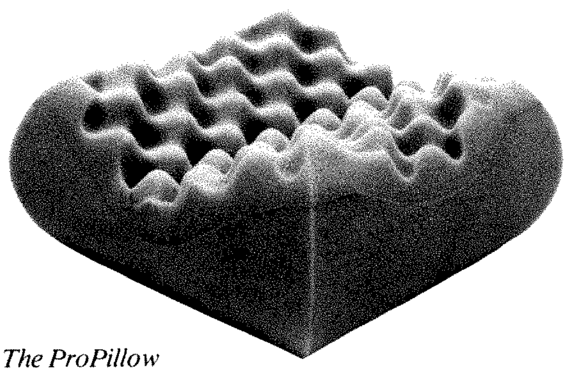
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

The ProPillow takes the pressure off

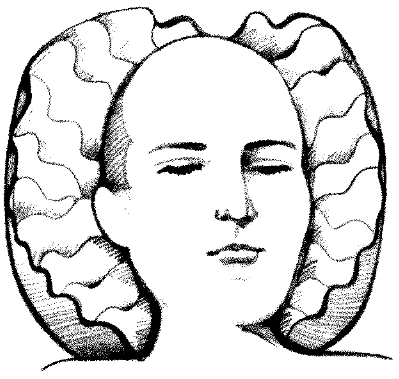
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



The ProPillow Anesthesia Pillow

The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.

An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

And the price is right

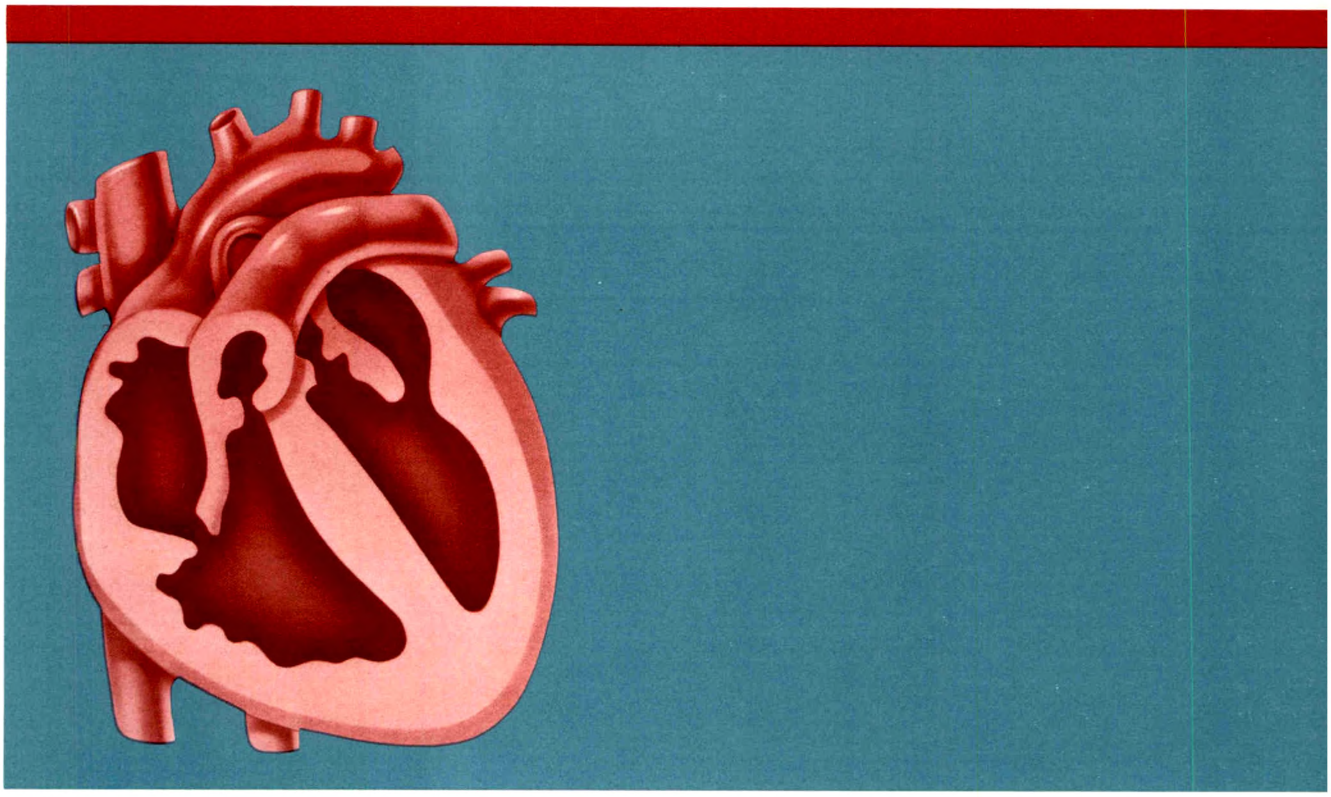
Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California**, or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

ProTechPacific
1221 Andersen Drive
San Rafael, CA 94901

Makers of the **ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXSEY Hip Abduction pillow** and the new **STRAPEZE ®Velcro Endotracheal Tube stabilizer.**

Special Benefits for Special Anesthetic Needs with Ēthrane® (enflurane)



For Myocardial Protection During Anesthesia

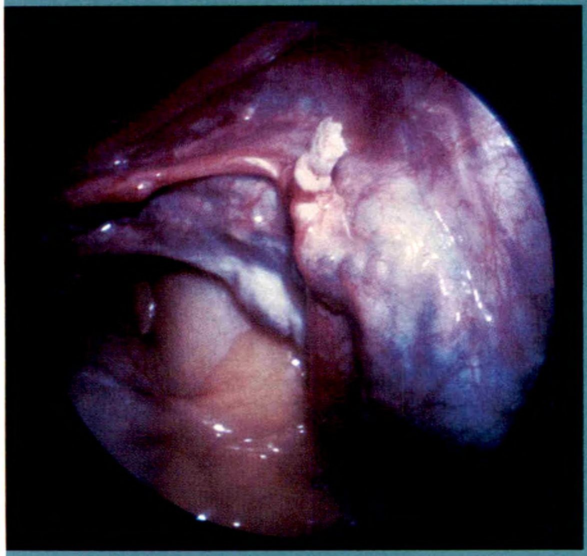
- **Decreases afterload,** to lessen myocardial work, especially in patients with coronary artery disease and/or hypertension (with adequate left ventricular function)
- **Helps maintain oxygen balance by decreasing myocardial contractility** (in patients with adequate left ventricular function)
- **Provides stability of heart rate and rhythm,** to help avoid transient increases in heart work

Anaquest

Ēthrane® (enflurane)

Special Benefits for Special Anesthetic Needs with Ēthrane®

(enflurane)

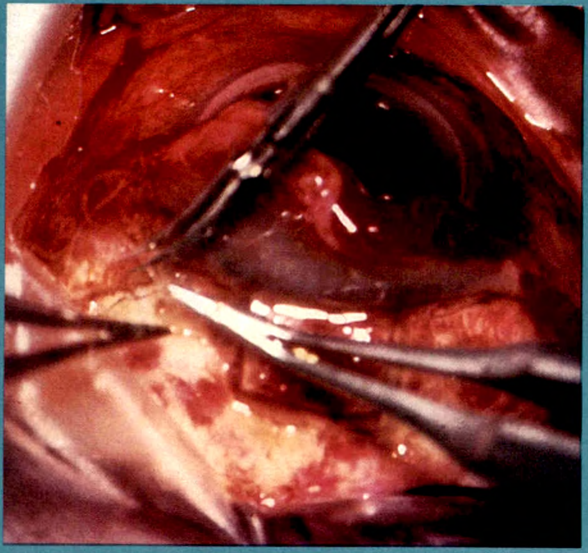


For Gynecological Surgery

- **Assured amnesia** at anesthetic concentrations
- **Prompt recovery** with little aftereffect, of special benefit in outpatient cases

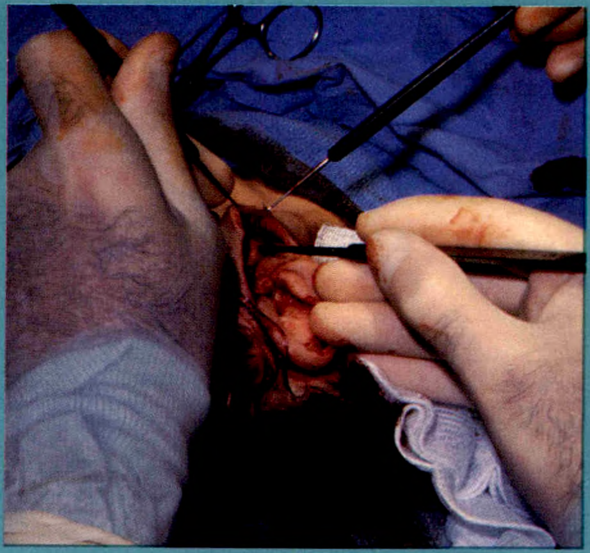
For Analgesia in Obstetrics

- **Prompt, controllable analgesia** at sub-anesthetic concentrations (0.25% to 1.0%)
- **Capability of nearly 100% oxygen delivery if needed; minimal postpartum base deficits in mother and newborn**
- **The only modern, potent inhalational agent approved for use in vaginal delivery**



For Intraocular Surgery

- **Consistent reduction and control of intraocular pressure,** consistent analgesia, and precise control of the depth of anesthesia
- **Smooth postoperative emergence**



In Oral, Maxillofacial and Plastic Surgery

- **Stability of heart rhythm**
- **Compatibility with epinephrine,** does not add to the arrhythmogenic potential of epinephrine needed for hemostasis
- **Low biodegradation,** only 2.4 percent of enflurane taken up during anesthesia is recovered as urinary metabolites

Ēthrane®...a product of original Anaquest research
(enflurane)

Anaquest Ēthrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without a Prescription.

DESCRIPTION

ĒTHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyi ether) (CHF_2OCF_2CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5 °C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20 °C, 218 at 25 °C and 345 at 36 °C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \qquad \begin{aligned} A &= 7.967 \\ B &= -1678.4 \\ T &= {}^{\circ}C + 273.16 \text{ (Kelvin)} \end{aligned}$$

The specific gravity (25 °/25 °C) is 1.517. The refractive index at 20 °C is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37 °C and the oil/gas coefficient is 98.5 at 37 °C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25 °C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ĒTHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide-30 percent oxygen, and 1.17 in 30 percent nitrous oxide-70 percent oxygen.

Induction and recovery from anesthesia with enflurane are rapid. Enflurane has a mild sweet odor. Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration. Enflurane reduces ventilation as depth of anesthesia increases. High $PaCO_2$ levels can be obtained at deeper levels of anesthesia if ventilation is not supported. Enflurane provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during enflurane anesthesia. Enflurane anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with enflurane and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), up to 2 micrograms per kilogram (2 μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period in patients judged to have ordinary tolerance to epinephrine administration. This would represent up to 14 ml of 1:100,000 epinephrine containing solution (10μg/ml), or the equivalent quantity, in a 70 kilogram patient. This may be repeated up to 3 times per hour (total 42 ml per hour). The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of enflurane.

Enflurane 0.25 to 1.0 percent (average 0.5 percent) provides analgesia equal to that produced by 30 to 60 percent (average 40 percent) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative, and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters serum BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane.

Analgetic doses of enflurane, up to approximately 1 percent, do not significantly depress the rate or force of uterine contraction during labor and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1 and 2 percent delivered enflurane; concentrations somewhere between 2 and 3 percent delivered enflurane may abolish uterine contractions. Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions; however, as the dose of enflurane progresses (somewhere between 1.5 and 3 percent delivered enflurane) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section; however, this has not been demonstrated within the recommended dosage range (see DOSAGE AND ADMINISTRATION section). Mean estimated blood loss in patients anesthetized for therapeutic termination of pregnancy with 1 percent enflurane in 70 percent nitrous oxide with oxygen is approximately twice that noted following therapeutic abortion performed with the use of a local anesthetic technique (40 ml versus 20 ml).

Pharmacokinetics: Biotransformation of enflurane in man results in low peak levels of serum fluoride averaging 15μM. These levels are well below the 50μM threshold level which can produce minimal renal damage in normal subjects. However, patients chronically ingesting isoniazid or other hydrazine containing compounds may metabolize greater amounts of enflurane. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50μM, particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in man in the absence of surgery. Thus enflurane does not depress this aspect of the immune response.

INDICATIONS AND USAGE

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

When previous exposure to a halogenated anesthetic is known to have been followed by evidence of unexplained hepatic dysfunction, consideration should be given to use of an agent other than enflurane.

PRECAUTIONS

General: ĒTHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

Information to Patients: Enflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 to 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for several days following administration.

Laboratory Tests: Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients.

Drug Interactions: The action of nondepolarizing relaxants is augmented by enflurane. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

Carcinogenesis/Mutagenesis: Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at ½, ⅛ and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ½ of 1%) but statistically significant increase in sperm abnormalities. In contrast to these results, in vitro approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguananine system) have not shown a mutagenic effect of enflurane.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when enflurane is adminsitered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/725,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g. enflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

1. Malignant hyperthermia (see PRECAUTIONS). 2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia. 3. Hypotension and respiratory depression have been reported. 4. Arrhythmias, shivering, nausea, and vomiting have been reported. 5. Elevation of the white blood count has been observed. 6. Unexplained mild, moderate and severe liver injury may rarely follow anesthesia with enflurane. Serum transaminases may be increased and histologic evidence of injury may be found. The histologic changes are neither unique nor consistent. In several of these cases, it has not been possible to exclude enflurane as the cause or as a contributing cause of liver injury. The incidence of unexplained hepatotoxicity following the administration of enflurane is unknown, but it appears to be rare and not dose related.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for enflurane;
b) vaporizers from which delivered flows can easily and readily be calculated.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3.0 percent enflurane. Maintenance concentrations should not exceed 3 percent. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Analgesia: Enflurane 0.25 to 1.0 percent provides analgesia for vaginal delivery equal to that produced by 30 to 60 percent nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

HOW SUPPLIED

ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.

125 ml—NDC 10019-350-50
250 ml—NDC 10019-350-60

Storage: Store at room temperature. Enflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised: 6/84

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019
Telex 910 286 2792
A Division of BOC Inc

Form No. 03-0164-A01 (Rev)
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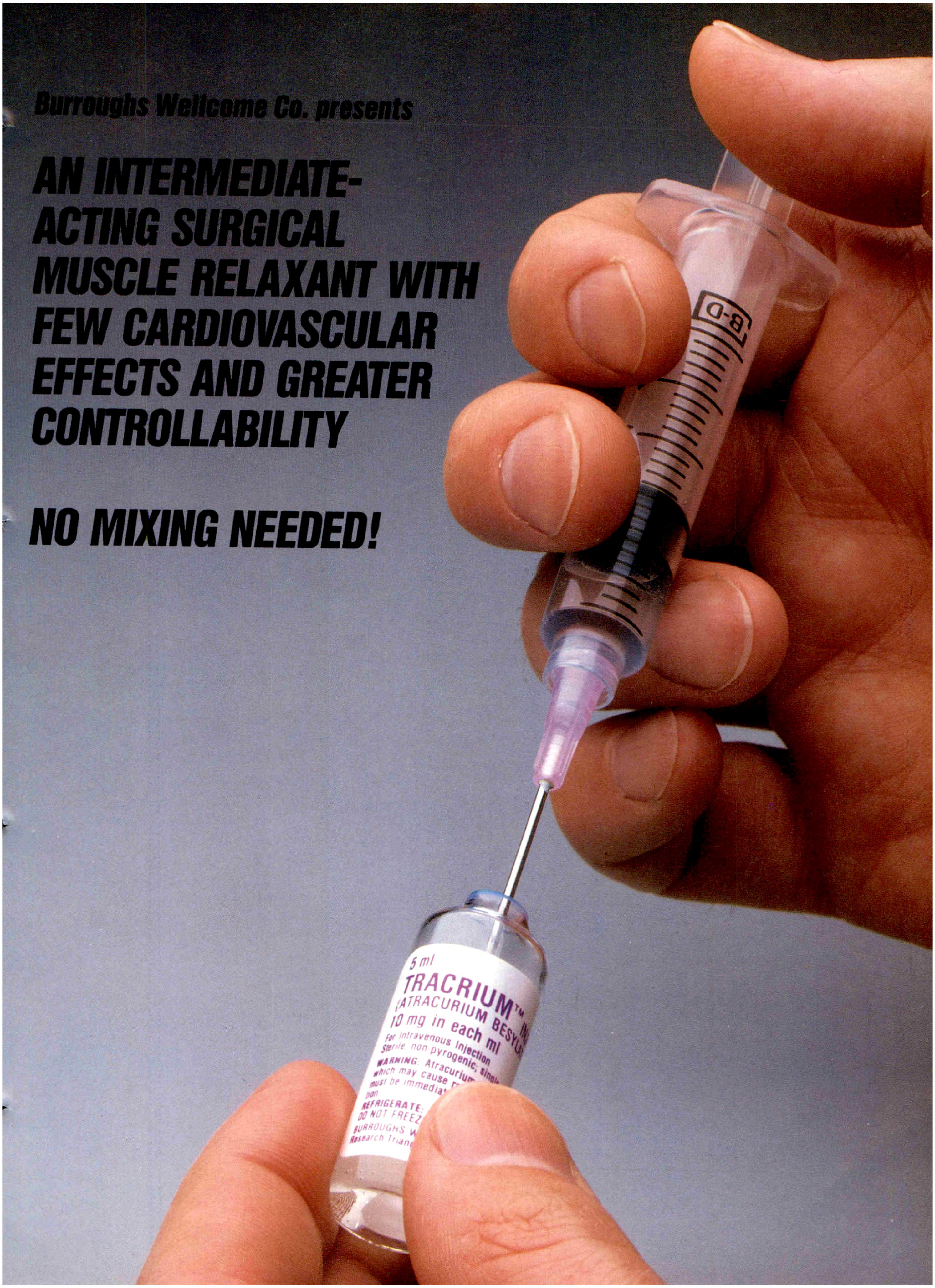
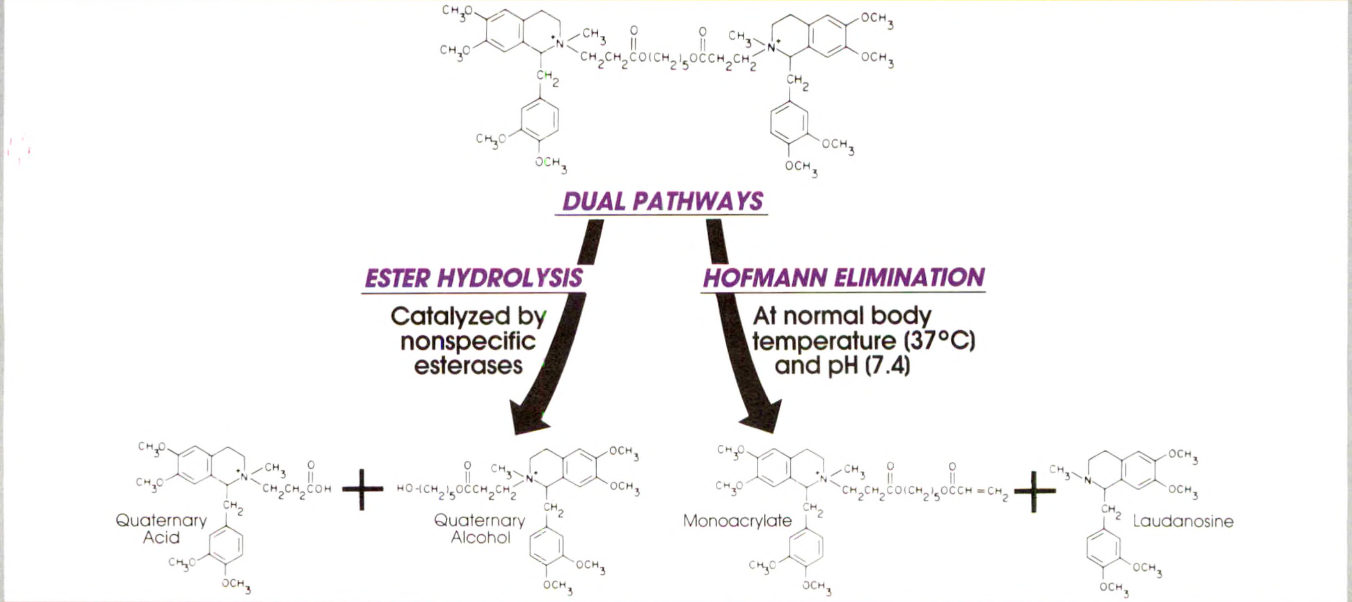
Burroughs Wellcome Co. presents

AN INTERMEDIATE-ACTING SURGICAL MUSCLE RELAXANT WITH FEW CARDIOVASCULAR EFFECTS AND GREATER CONTROLLABILITY

NO MIXING NEEDED!



UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH

2 Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required

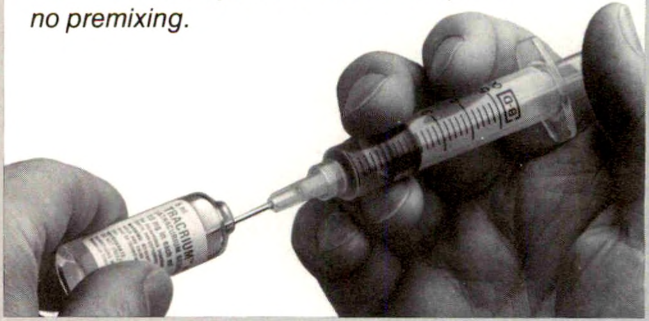
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

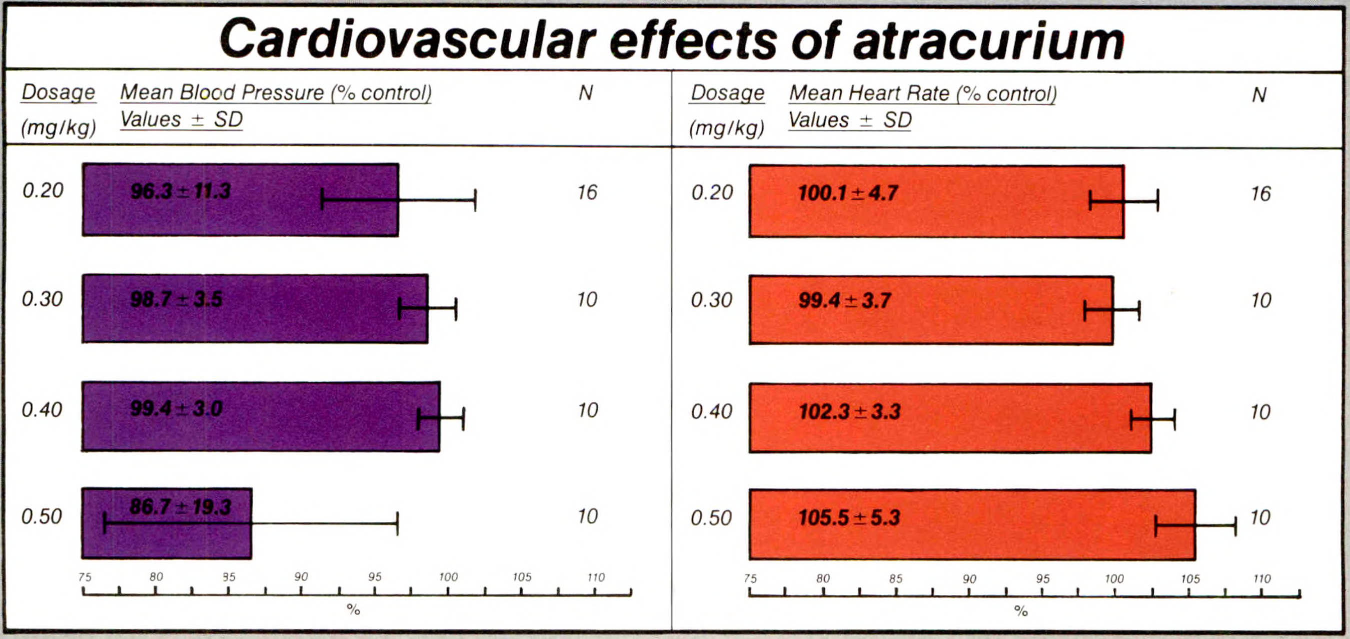
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.


Cardiovascular effects of atracurium

Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium[4]

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

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1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
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TRACRIUM® INJECTION
(atracurium besylate)

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TRACRIUM® INJECTION
(atracurium besylate)

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507

Printed in U.S.A.

TRACRIUM® INJECTION
(atracurium besylate)
TELECONFERENCE

March 20, 1985

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TRACRIUM INJECTION
(atracurium besylate)

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Regonol®

(pyridostigmine bromide injection)

Now formulated without parabens, Regonol is a fast-acting reversal agent with documented advantages over neostigmine. It maintains greater cardiovascular stability,[1] causes fewer muscarinic side effects,[2] and has up to 33% longer action.[2] A wider margin between the anti-curare dose and the neuromuscular blocking dose[2] assures better control of the patient.

A step forward in reversal exclusively from Organon

25 mg in a 5 ml vial
(5 mg/ml)

References: 1. Gyermek L: *Curr Ther Res* 18:377-386, 1975. **2.** Katz RL: *Anesthesiology* 28:528-534, 1967.

BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents: intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg.) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED—Regonol is available in:
5 mg./ml.: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

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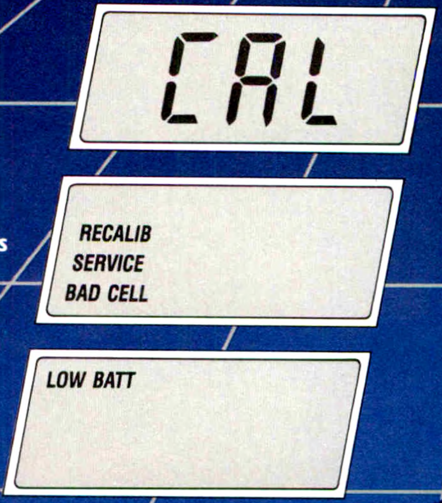

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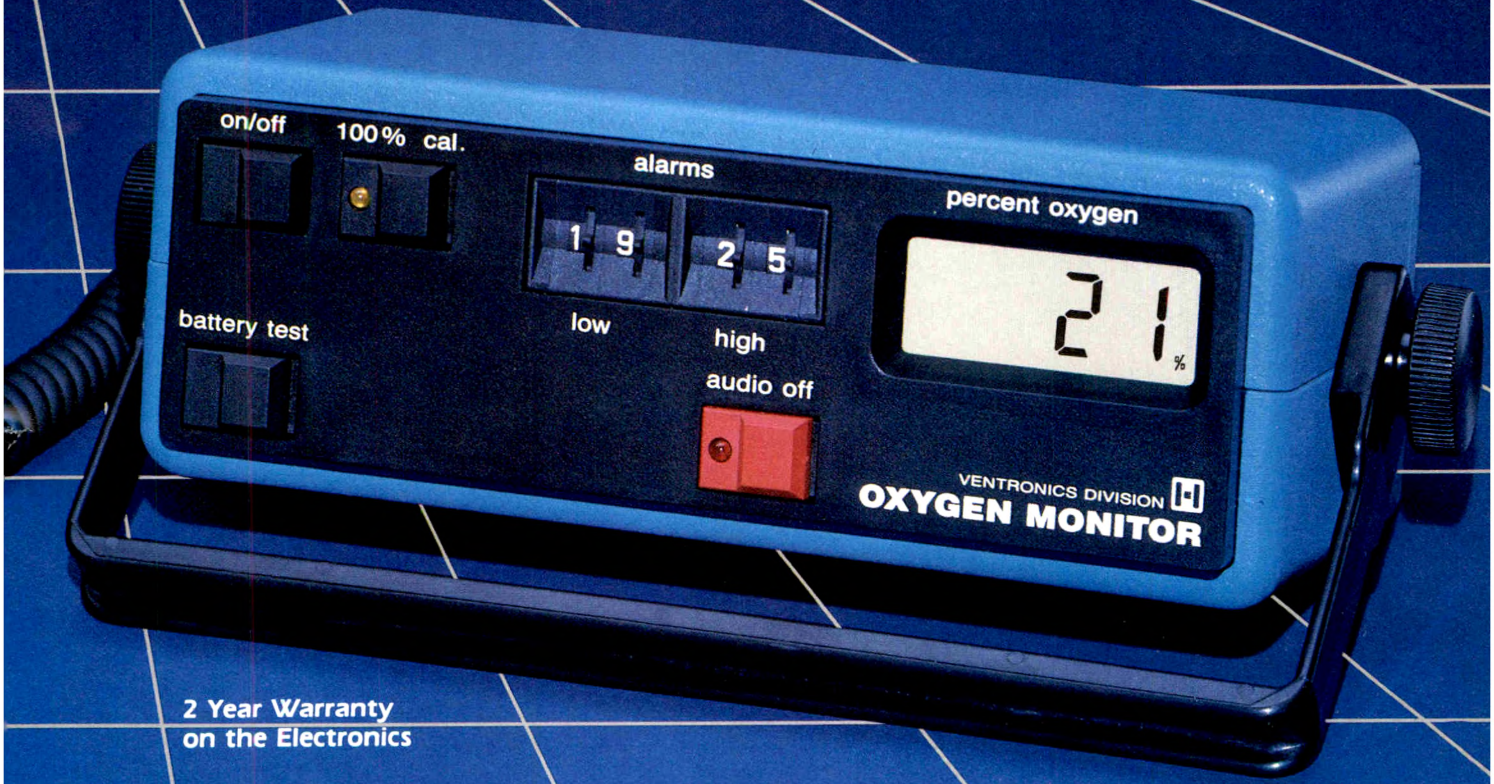

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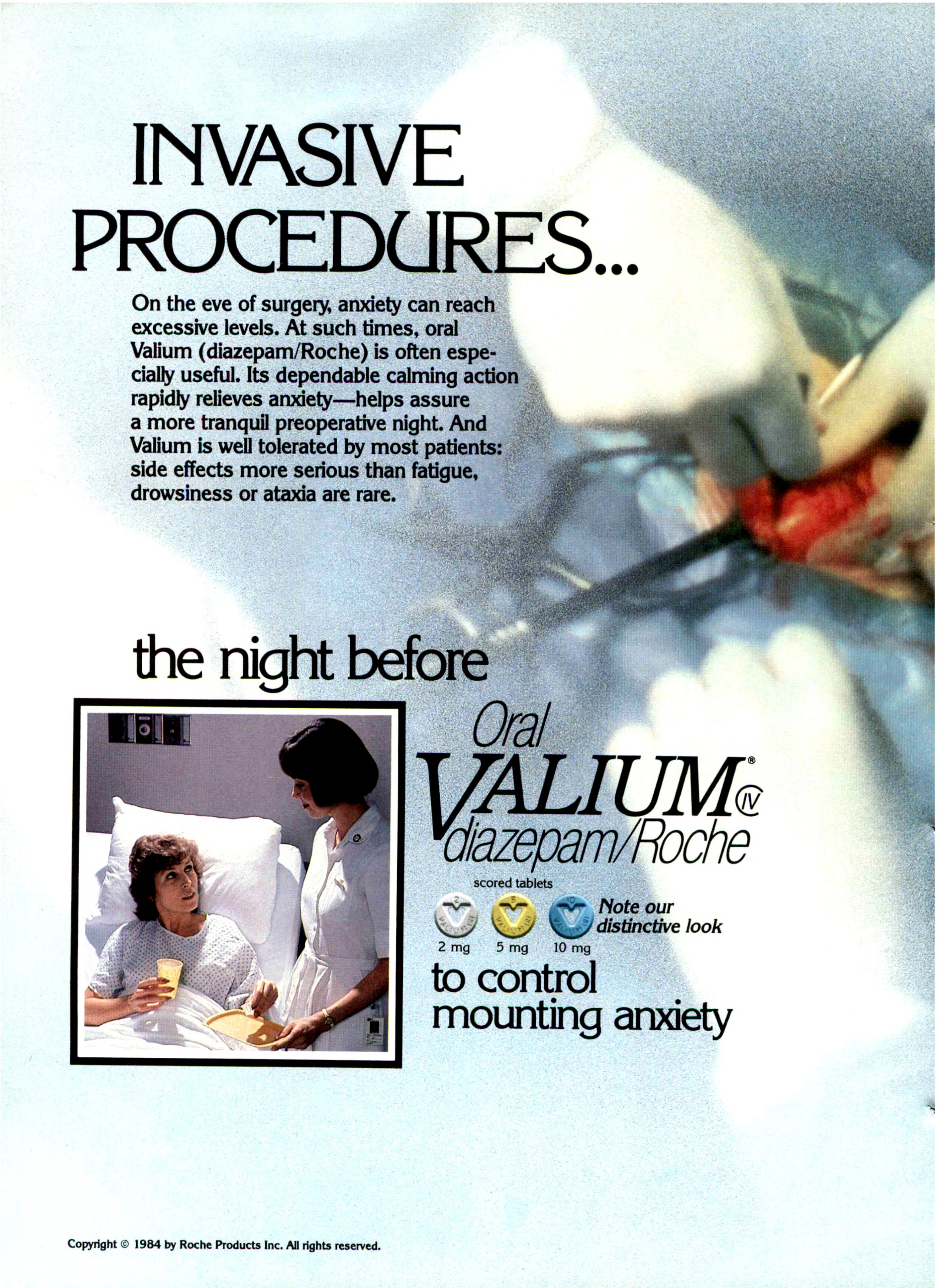

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the night before

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to control mounting anxiety

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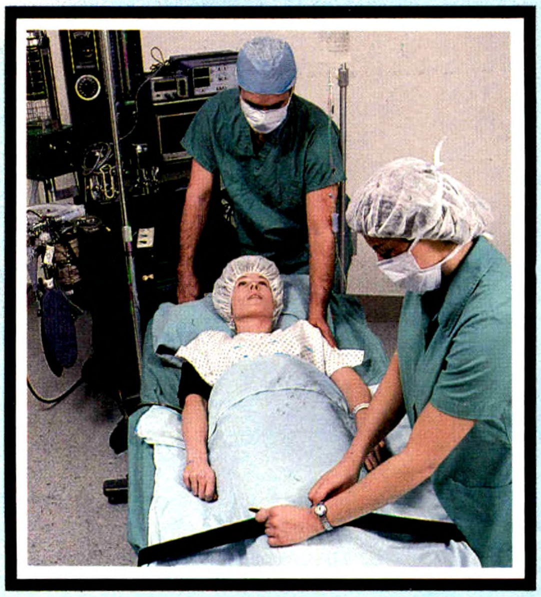
minutes before

Injectable
VALIUM*® *I.V.
diazepam/Roche (IV)



to control anxiety and diminish recall

See next page for references and a summary of product information.

References: 1. Diazepam and lorazepam in anaesthesia. *Drug Ther Bull 17*(5):19-20, Mar 2, 1979. **2.** Conner JT, *et al: J Clin Pharmacol 18:*285-292, May-Jun 1978. **3.** George KA, Dundee JW: *Br J Clin Pharmacol 4:*45-50, Feb 1977. **4.** Dundee JW, Pandit SK: *Br J Pharmacol 44:*140-144, Jan 1972. **5.** Dundee JW, *et al: Br J Anaesth 51:*439-446, May 1979. **6.** Gregg JM, Ryan DE, Levin KH: *J Oral Surg 32:*651-664, Sep 1974.

Injectable Valium® (diazepam/Roche) Ⓒ
Valium® (diazepam/Roche) Ⓒ

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications: Tablets in children under 6 months of age; known hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of predisposition to habituation/dependence.

> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

ORAL: Advise patients against simultaneous ingestion of alcohol and other CNS depressants.

Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.* Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least ⅓, administer in small increments.

Injectable Valium® (diazepam/Roche)
Valium® (diazepam/Roche)

Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs.

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status. Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium, *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed and tolerated).

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

INJECTABLE: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium therapy and are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension. Dialysis is of limited value.

How Supplied

ORAL: Round, scored tablets* with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500; Prescription Paks of 50, available in trays of 10. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

INJECTABLE:† Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10.

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PLEASE CONSULT FULL PRESCRIBING INFORMATION: A SUMMARY FOLLOWS:

CONTRAINDICATIONS: MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type. The following conditions preclude the use of spinal anesthesia: (1) Severe hemorrhage, severe hypotension, or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output; (2) Local infection at the site of proposed lumbar puncture; (3) Septicemia.

WARNINGS: LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE** AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid while performing spinal anesthesia indicates entry into the subarachnoid space. Aspiration should be performed before the anesthetic is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because severe, persistent hypertension may occur. MARCAINE solutions containing a vasoconstrictor such as epinephrine should be used cautiously in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Administration of MARCAINE to patients younger than 18 years is not recommended, nor is the mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE because of insufficient data on the clinical use of such mixtures.

PRECAUTIONS: General: The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patients should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anesthetic injection should be constantly and carefully monitored. Restlessness, anxiety, incoherent speech, light-headedness, numbness, and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used cautiously in patients with severe disturbances of cardiac rhythm, shock or heart block.

Sympathetic blockade during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should also be carefully monitored because it is not always controllable in spinal techniques.

Because the liver metabolizes amide-type local anesthetics such as MARCAINE, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used cautiously in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than those in other major blocks; most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be considered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It is not known whether amide-type local anesthetics trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome depends on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending on the physician's evaluation of the situation and ability to deal with possible complications or complaints: (1) Preexisting diseases of the central nervous system, such as those resulting from pernicious anemia, poliomyelitis, syphilis, tumor; (2) Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage; (3) Chronic backache and preoperative headache; (4) Hypotension and hypertension; (5) Technical problems (persistent paresthesias or bloody tap); (6) Arthritis or spinal deformity; (7) Extremes of age; (8) Psychosis or other causes of poor cooperation by the patient.

Information for Patients: Patients should be informed that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

Clinically Significant Drug Interactions: Local anesthetic solutions containing epinephrine or norepinephrine administered to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided but, when necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals of most local anesthetics including bupivacaine to evaluate carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic, or mutagenic or that it impairs fertility.

Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of bupivacaine's effect on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See **Labor and Delivery.**)

Labor and Delivery: Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Regional anesthesia has produced maternal hypotension. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may result in diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

Cardiac arrest has been reported during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The MARCAINE hydrochloride package insert for epidural, nerve block, etc. discusses this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for obstetrical spinal anesthesia. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

Nursing Mothers: It is not known whether local anesthetic drugs are excreted in human milk; therefore, caution should be exercised when local anesthetics are administered to a nursing woman.

Pediatric Use: Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

ADVERSE REACTIONS: Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences following spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Respiratory System: Respiratory paralysis or underventilation may result from upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation may contribute to underventilation. This will usually occur within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, intercurrent drug use, and surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood and interstitial fluid volumes, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injections may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

Neurologic: Adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also depend on the particular drug used, the route of administration and the physical status of the patient. Many effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus; arachnoiditis; slowing of labor, increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; fecal and urinary incontinence.

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions include urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

Other: Nausea and vomiting may occur during spinal anesthesia.

OVERDOSAGE: Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone or contributory mechanical obstruction of venous return.

Management of Local Anesthetic Emergencies: The first consideration is prevention through careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. Administer oxygen at the first sign of change.

The first step in managing systemic toxic reactions, as well as underventilation or apnea due to a high or total spinal is to ***immediately*** *establish and maintain a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after instituting these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation.

Hypotension due to sympathetic relaxation may be managed with intravenous fluids, in an attempt to relieve mechanical obstruction of venous return or by using vasopressors and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the physician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in maintaining a patent airway or if prolonged ventilatory (assisted or controlled) support is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD_{50} in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

Composition of MARCAINE Spinal Solutions: Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C, and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

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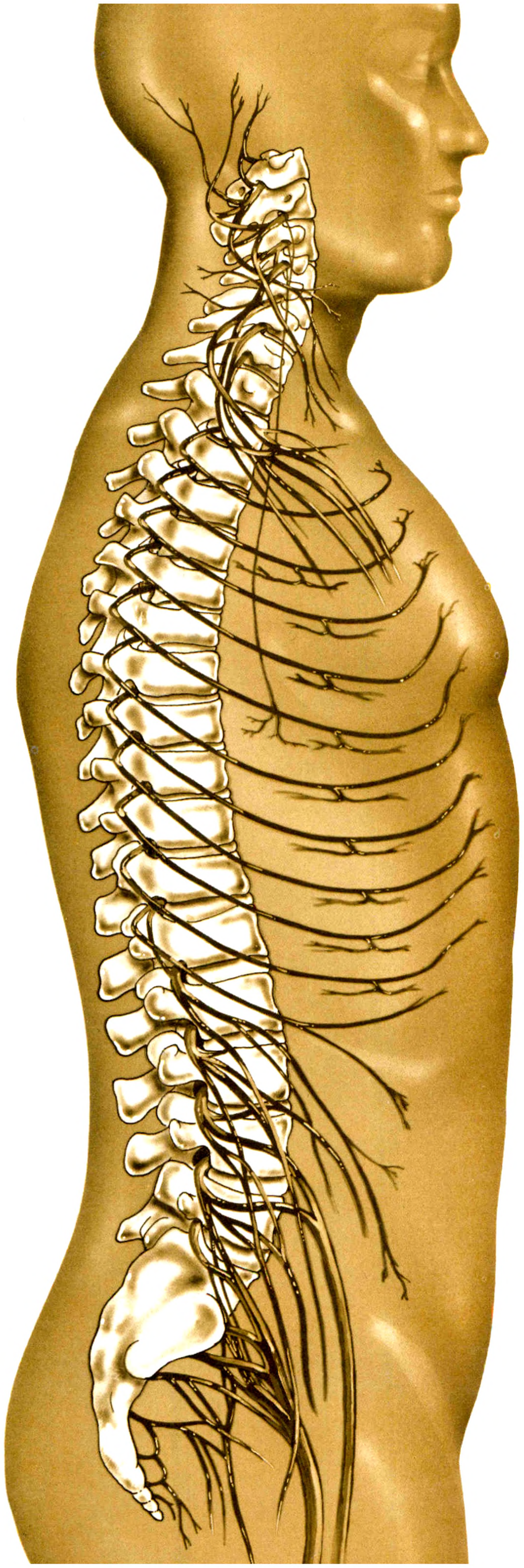

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Reference:
1. Moore DC: Spinal anesthesia: Bupivacaine compared with tetracaine. *Anesth Analg* 1980; 59:743-750.

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I.A.R.S. 59th CONGRESS—MARCH 9–13, 1985
ADAM'S MARK HOTEL—HOUSTON, TEXAS

SCIENTIFIC PROGRAM SUMMARY: 26 Review Course Lectures; 2 Panel Presentations; 8 Theme Luncheons; 114 Scientific Papers; Exhibits;

T. H. Seldon Distinguished Lecture: *''Standards for Excellence''*—M. T. Jenkins, M.D.

MEETING SCHEDULE:

Saturday, March 9:	Registration—1 to 7 p.m. (Continues throughout meeting)
Sunday, March 10:	
8–5 PM	Review Course Lectures
9–12 PM	Panel—''Cardiac Anesthesia—Case Discussions''
2–5 PM	Panel—''Impact of Legislation and Regulation on Economics in Anesthesiology''
12–5 PM	Scientific and Technical Exhibits Open
6–7 PM	Complimentary Informal Reception
Monday, March 11:	
8–12 PM	Three Concurrent Sessions: Room 1—Review Course Lectures; Rooms 2 and 3—Scientific Papers
1:15–2 PM	T. H. SELDON DISTINGUISHED LECTURE
2–5 PM	Three Concurrent Sessions (as above)
9–3 PM	Scientific and Technical Exhibits
Tuesday, March 12:	
8–5 PM	Three Concurrent Sessions (as above)
12–2 PM	Four Concurrent Theme Luncheon Sessions
12–5 PM	NASA Tour
9–1 PM	Scientific and Technical Exhibits (Final Day of Exhibits)
Wednesday, March 13:	
8–5 PM	Three Concurrent Sessions (as above)
12–2 PM	Four Concurrent Theme Luncheon Sessions

REGISTRATION FEES: Amounts shown include choice of all sessions except Theme Luncheons ($12 each) and NASA Tour ($19.50 including box lunch)

I.A.R.S. Members and Associate Members:	$150—pre-registration ($175 on site)
I.A.R.S. Educational Members:	NO FEE
Non-I.A.R.S. Members:	$175—pre-registration ($200 on site)
Non-member Residents, Students:	$25 (with certification from Program Director)

CME CREDITS: As an organization accredited for continuing medical education by ACCME, the I.A.R.S. designates this activity as Category 1 of the Physicians Recognition Award. One credit hour may be claimed for each hour of participation, up to a maximum of 31 hours. AANA—Prior approval pending for 31 AANA credits.

PRE-REGISTRATION MAILING

The preliminary program showing daily schedule; hotel card; Delta Airlines special fare information for U.S. registrants; and schedule of social activities for guests and registrants will be mailed in mid-December to all I.A.R.S. members. Enrollment forms for Theme Luncheons NASA Tour and Social Program will be sent only to those who pre-register for the meeting, and will be assigned on a first-come basis. Non-members may receive material by writing to:

International Anesthesia Research Society
3645 Warrensville Center Rd., Cleveland, Ohio 44122
(Tel: (216) 295-1124 or 295-1130)

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1985;64:95–100

Noninvasive Assessment by Radiotelemetry of Antacid Effect during Labor

Geraldine M. O'Sullivan, MB, FFARCS, and Roy E. Bullingham, MB, FFARCS

O'SULLIVAN GM, BULLINGHAM RE. Noninvasive assessment by radiotelemetry of antacid effect during labor. Anesth Analg 1985;64:95–100.

A noninvasive radiotelemetry technique was used to study the antacid effect of 15 ml of 0.3 M sodium citrate in 26 women in established labor. The subjects swallowed a pH radio pill, whose signal was detected transabdominally by a radio receiver. The median and range of values for the time to return to the preantacid basal pH for all of the women in labor was 84.0 (11.8–195.8) min. However, there was a significant difference ($P < 0.05$) in the duration of action of sodium citrate between the women who had received no analgesia and those given intramuscular meperidine. The median and range of values for the time to return to the preantacid basal pH in patients who had received meperidine during labor was 166.0 (147.7–195.8) min, whilst in those who had received no analgesia the values were 56.7 (11.8–143.0) min. There were no significant differences between patients given no analgesia and those given extradural analgesia. Pretreatment with intravaginal prostaglandins (PGE_2) did not influence antacid effect.

Key Words: GASTROINTESTINAL TRACT—antacids. ANESTHESIA—obstetrics.

Numerous preventative and prophylactic measures are practiced in an attempt to reduce the risk of acid pulmonary aspiration (Mendelson's syndrome) (1) during labor and delivery. These include prohibition of solid food during labor, preoperative emptying of the stomach, oral administration of antacids during labor with an additional bolus prior to surgery, and the use of cricoid pressure during the induction of general anesthesia. More recently, the use of H_2 receptor antagonists during labor and before cesarean section (2,3) has been suggested.

The severity of Mendelson's syndrome is a function of the pH and volume of the aspirated fluid (4,5). In the past, because antacids did not always appear to provide protection against the effect of aspiration (6,7), larger volumes and their more frequent administration during labor were advocated (8,9). The known pulmonary toxicity associated with the aspiration of antacids (10), the severity of which appears to depend upon the volume aspirated (11), and the failure to improve maternal mortality despite the use of repeated doses of antacids (12) cast doubt on the validity of administering antacids prophylactically throughout labor.

A recent study (13) using a noninvasive radiotelemetry technique demonstrated a wide variation in the efficacy and duration of action of both particulate and nonparticulate antacids. Nor was any difference found in antacid effect between pregnant and nonpregnant women (14). In addition, doubling the volume of the nonparticulate antacid 0.3 M sodium citrate from 15 ml to 30 ml was not found to produce a significantly greater effect (15). These studies did, however, indicate that one of the main factors determining the duration of antacid action was the rate of gastric emptying. During labor, antacid efficacy might differ from that in nonlaboring pregnant women, because of the gastrointestinal effects of labor itself, the associated pain, and the concomitant use of analgesics, prostaglandins, or oxytocics. In this study, a noninvasive radiotelemetry technique was applied to assess antacid efficacy during established labor.

Materials and Methods

Radiotelemetry Equipment

The radiotelemetry system has three main components: a pH radio pill (Model 7006, Medici Developments Ltd, London); an aerial; and a receiving system (16). The pH pill, which measures approximately 28

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Address correspondence to Dr. O'Sullivan, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headington, Oxford OX3 9DU, England.

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mm by 7.2 mm, consists of a glass case that contains a transducer, a replaceable mercury battery (Ray-O-Vac R212, 1.4 V), and a small encapsulated radio transmitter. A pH-sensitive glass bulb is fused to one end of the pill, and a replaceable reference electrode is inserted into the opposite open end of the pill. This electrode is contained in a silicone rubber moulded cap and consists of a silver–silver chloride disc and a salt bridge. Changes in pH are detected by the electronic assembly and the signal is received by inductive coupling to an aerial that is connected to a radio receiver designed for reception in the frequency range 285–525 kHz. The receiver unit measures 27 cm by 12 cm by 15 cm and weighs 3 kg. Radio pills transmit very low power (less than one mW) and at a distance of more than 1 m it is very difficult to receive the signal without interference. The receiver also monitors the signal strength from the pill, which allows optimum positioning of the aerial, thereby preventing the appearance of artifact in the recorded trace due to a critical decline in signal strength. After activation of the pill in 0.1 M HCl and of the reference electrode in a saturated saline solution, the pills were assembled and calibrated. Calibration was performed at 37°C in a thermostatically controlled water bath, using buffers of known pH (2 and 7 [Fisons, Burroughs-Wellcome]). A buffer solution of pH 4 was used to check the linearity of the pH pills. The pH measurements of the pill are linear (± 0.2 pH) over the pH range 1–9. The pill reaches 95% of the final recorded value in 1 sec, and the temperature coefficient of the pH pill is approximately 0.1 pH/°C. A chart recorder (MX2, Lectromed Ltd) was connected to the radio receiver to provide a permanent record for each subject.

0.3 M Sodium Citrate (SCT)

This solution was prepared in the hospital pharmacy by dissolving 88.23 g of trisodium citrate in 1 L of chloroform water. The solution also contains 10 ml of concentrated anise water (BPC), and the pH of the solutions used varied between 8.0 and 8.5. The solutions, which were replaced at two monthly intervals, were stored in a sealed plastic container in a refrigerator.

Clinical Studies

The efficacy of the nonparticulate antacid sodium citrate 0.3 M was assessed in 26 women in established labor. The study was approved by the Central Oxford Research Ethics Committee. In order to obtain fully informed consent, patients presenting for induction of labor were chosen and the study was explained to them on the afternoon before induction. The principal indication for the induction of labor was the occurrence of a postterm pregnancy, but labor was induced in two patients because of an increase in blood pressure at term. In two patients, induction of labor proved unnecessary when labor began spontaneously. Women considered by the obstetricians to have a cervix unfavorable for induction of labor were pretreated with 2.5 mg of PGE_2 in a glyceride-based pessary (Witepsol E75). After amniotomy, labor was further augmented with oxytocin if required. All the subjects received a light breakfast (bread roll and tea), and in accordance with the regime of the labor ward, only sips of water were allowed during the course of labor. The study was not started in any patient until labor was well established, and thus no study was started until cervical dilatation had reached at least 4 cm. Analgesia of the patient's choice, which could include the use of extradural analgesia, meperidine, or premixed nitrous oxide–oxygen (Entonox), was administered as required during labor. The study was performed in the position that was most comfortable for the patient, most frequently the sitting or the left lateral position. This is in contrast to the previous radiotelemetry studies (14,15) in pregnant women in which the subjects lay in the left lateral position in order to prevent the too rapid evacuation of the pill from the stomach. The women were allowed 15–30 ml water to facilitate swallowing of the pH pill. When a stable pH baseline had been reached, 15 ml of sodium citrate was administered. Recordings were continued until the pH had returned to the preantacid baseline, continuing throughout the second and third stages of labor if necessary.

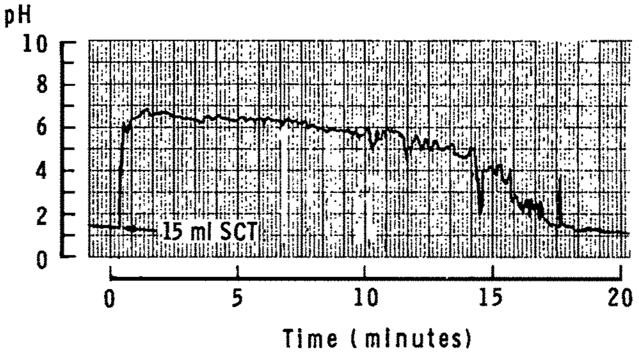

Figure 1. Intragastric pH change after the administration of 15 ml of 0.3 M sodium citrate (SCT) to a woman in labor.

Measurements and Analysis

As in the previous telemetry studies (13–15), the following indices were either measured or derived from the recorded tracings: the initial resting pH value, the maximum pH reached after the administration of the antacid, the time taken to reach the maximum pH value, the time taken for the pH to decrease 1 pH unit from the maximum pH, the duration of time the pH remained above 3.0, the time taken for the pH to return to the initial pH value ± 0.5 pH unit, the time taken for the pH to decrease to half of the maximum pH change ($t_{1/2}$), and the difference between the times taken for the pH to fall to 90% and 10% of the peak value ($t_{0.1-0.9}$). The integrated area under the curve of pH against time (AUC) was used as a measure of in vivo antacid efficacy and the units of measurement of this curve are pH·min (Fig. 1). The Kruskal Wallis and the Mann–Whitney *U*-tests were used to evaluate statistical significance.

Table 1. Values after the Administration of 15 ml of 0.3 M Sodium Citrate to Women in Labor

	Median	Range
Number of women studied	26	
Basal pH	2.0	1.4–2.5
Maximum pH	6.8	5.4–7.9
Time to peak pH (min)	1.0	0.2–2.8
Time to decrease 1 pH unit from peak (min)	30.7	3.3–154.0
AUC (pH·min)	207.8	34.1–630.3
Time pH > 3.0 (min)	61.5	10.0–190.8
$t_{1/2}$ (min)	47.0	6.3–187.5
$t_{0.1-0.9}$ (min)	69.3	6.2–186.6
Time to return to basal pH (min)	84.0	11.8–195.8

Results

The mean ± SEM values for the age, weight, and height of the women in labor were 28.4 ± 1.2 yr, 77.1 ± 2.6 kg, and 1.63 ± 0.01 m, respectively. The mean basal pH was 2.0 ± 0.06. Four of the 26 women were primiparae, and 17 women were pretreated with PGE_2. During the course of labor, 17 women required no analgesia until the end of the first stage when eight of these women used premixed nitrous oxide–oxygen. Of the remaining nine women, five had extradural analgesia and four were given intramuscular meperidine (100 mg) and promethazine (25 mg). Two of the women who had received no analgesia vomited during the study, and only the data up to the time of emesis have been included. The pH pill left the stomach before the return to the preantacid baseline of three of the subjects who had received no analgesia and in one of the subjects who had been given meperidine; such data as are available from these three patients have been included as appropriate.

Table 1 illustrates the effects of administering 15 ml of sodium citrate to women in labor. Table 2 shows the results divided into groups determined by the mode of analgesia used during the course of labor. There was a statistically significant difference for some of the measures of antacid duration between the group who had received no analgesia and those who had received meperidine. The median time to return to the preantacid basal pH was 166.0 min in those who had meperidine compared to 56.7 min in those who had no analgesia. There were no statistically significant differences between patients given no analgesia and those given extradural analgesia. Table 3 shows the results of the patients who had received no analgesia and who have been subdivided into groups, depending upon whether they had been pretreated with PGE_2 pessaries. No significant differences were found between the two groups.

Discussion

The use of a radiotelemetry technique during labor allows gastric acidity to be measured accurately throughout labor and delivery. This study was performed in women who were in established labor, many of whom were being monitored for obstetric purposes. Although patient acceptance of the radiotelemetry technique was excellent, the recently developed small portable radio receivers (17) could even circumvent the restrictions on ambulation necessary with the present equipment.

During labor, the values relating to the preantacid residual volume and gastric secretion (basal pH and maximum pH) had similar medians and ranges to the values previously reported in women in the third trimester of pregnancy (15). The median values for antacid efficacy (AUC) and duration of action during labor were larger (though not significantly) than the values seen in nonlaboring women. The ranges of the measurements were also wider in labor; in particular, the upper range of the values recorded was about twice that of the women not in labor. Thus some women in labor are likely to obtain considerably more effect from antacid than volunteer studies would suggest, and Table 2 suggests that this is mainly due to the techniques used to relieve pain during labor.

There was a significant difference ($P < 0.05$) for most of the measurements of dynamic antacid effect, i.e., the time required to return to the preantacid baseline, the time pH was > 3.0 and the $t_{0.1-0.9}$ value, between the subjects who had received no analgesia and those who had been given meperidine. Although only four patients received meperidine, the effect was sufficiently marked so that nonparametric statistical methods (18) were able to distinguish these differ-

Table 2. Median and Range of Values after the Administration of 15 ml of 0.3 M Sodium Citrate to Women in Labor

	No analgesia	Extradural	Meperidine
Number of women	17	5	4
Basal pH	1.9 (1.4–2.5)	1.9 (1.5–2.1)	2.1 (1.9–2.4)
Maximum pH	6.8 (5.4–7.9)	6.8 (6.0–7.3)	7.0 (6.0–7.6)
Time to peak pH (min)	0.9 (0.2–2.8)	1.1 (0.6–2.2)	0.8 (0.3–1.6)
Time to decrease one pH unit (min)	15.8 (3.3–80.7)	35.0 (4.0–50.5)	49.4 (26.2–154.0)
AUC (pH·min)	192.3 (34.1–409.0)	327.2 (50.0–376.9)	374.0 (259.6–630.3)
Time pH > 3.0 (min)	51.7[a] (11.0–142.8)	102.8 (10.0–160.8)	161.5[a] (126.3–190.8)
$t_{1/2}$ (min)	42.7 (9.1–111.3)	81.5 (6.3–106.6)	80.5 (58.2–187.5)
$t_{0.1-0.9}$ (min)	44.3[a] (7.5–124.5)	96.6 (6.2–159.7)	141.3[a] (125.0–186.6)
Time to return to basal pH (min)	56.7[a] (11.8–143.0)	109.0 (13.3–177.0)	166.0[a] (147.7–195.8)

[a] Significant difference ($P < 0.05$) between the patients who had received no analgesia and those who had received meperidine.

ences. Although not statistically significant, the women in labor who had received extradural analgesia also had a longer duration of antacid action than the women who had received no analgesia. The previous telemetry studies (13–15) assessing antacid effect in pregnant and nonpregnant subjects indicated that gastric emptying was one of the principal factors determining the duration of action of antacids. From the known effects of opiates on the gastrointestinal tract (19), the prolongation of antacid effect in those subjects given parenteral analgesia could perhaps have been predicted. The delay in gastric emptying, with the consequent alteration of antacid duration of action, caused by the use of extradural analgesia, was less than that caused by narcotic analgesia, a feature supported by previous studies comparing the effects of narcotic analgesia and extradural analgesia on the gastrointestinal tract (20).

This study thus suggests that although there may be a slight delay in gastric emptying during labor, it is greatly accentuated by the effect of meperidine and to a lesser extent by extradural analgesia. Previous studies on gastric emptying during labor are, possibly because of the variety of techniques used, somewhat conflicting but generally support these findings. In two separate x-ray studies of gastric emptying in labor (the first (21) in which the women had received no medication and the second (22) in which medications are not mentioned), only three women from the total of 22 studied demonstrated a delay in gastric emptying. Yet another x-ray study (23) demonstrated that labor plus analgesia (meperidine 100 mg, scopolamine 0.4 mg) resulted in a greater delay in gastric emptying relative to the delay seen in third trimester patients who had received the same medication. Utilizing the kinetics of oral paracetamol absorption (24) as an indirect method of assessing gastric emptying (which method relies on the rapid absorption of paracetamol from the upper small intestine), labor alone was shown to cause a minimal delay in gastric emptying. However when narcotic analgesics were administered there was a very marked inhibition of gastric emptying; the mean maximum plasma concentration was not reached until 4 hr after ingestion in the patients who had received meperidine (100–150 mg) as compared to 30 min in women early in labor who had received no analgesia. In contrast, one study using a 750 ml water test meal (25) in women who had not received analgesia, demonstrated both a marked delay in gastric emptying during labor and an alteration from the normal exponential pattern of evacuation of liquids from the stomach.

Although it is the methylated prostaglandin analogues that cause the greatest decrease in gastric secretion (26), several of the natural prostaglandins such as PGE_1 and PGE_2 inhibit gastric acid secretion in animals and humans when given parenterally but are inactive or weak if given orally (27). PGE_2 has been shown to lower gastro–esophageal sphincter pressure, but it does not significantly alter gastric motility (28). PGE_2 is rapidly absorbed from the vagina, and systemic plasma concentrations are maintained for several hours, although considerable patient variation occurs (29). The effect on the gastrointestinal tract of

Table 3. Efficacy and Duration of Action of 15 ml of 0.3 M Sodium Citrate in the Subjects Receiving No Analgesia during Labor and Who Either Were or Were Not Pretreated with Vaginal PGE_2 Pessaries

	PGE_2	No pretreatment	*P* value
Number	10	7	
Basal pH	1.8 (1.4–2.5)	2.1 (1.8–2.5)	NS
Maximum pH	6.7 (5.4–7.7)	7.3 (6.2–7.9)	NS
Time to peak pH (min)	1.0 (0.4–2.7)	0.9 (0.2–2.8)	NS
Time to decrease 1 pH unit (min)	14.0 (3.3–80.7)	23.0 (10.1–61)	NS
AUC (pH·min)	191.0 (34.1–409.0)	193.6 (58.0–354.3)	NS
Time pH > 3.0 (min)	49.9 (11.0–117.4)	55.0 (15.5–142.8)	NS
$t_{1/2}$ (min)	44.6 (12.4–111.3)	40.8 (9.1–105.5)	NS
$t_{0.1-0.9}$ (min)	35.0 (7.5–89.0)	68.5 (12.3–124.5)	NS
Return to basal pH (min)	55.0 (11.8–128.0)	77.3 (19.8–143.0)	NS

Values are medians and ranges. NS, not significant.

prostaglandins given vaginally has not been studied, but their potential influence cannot be ignored. In this study, no difference was demonstrated between the patients who had or had not received PGE_2 but, given the large variation in the absorption from intravaginal prostaglandin pessaries, controlled studies would be required to elucidate definitively the effect of PGE_2 on the upper small intestine during labor.

Any factor likely to alter gastric emptying is relevant if antacids are to be regularly administered throughout labor. Frequent antacid administration in the patients who have received opiate analgesia could result in an accumulating intragastric volume that may predispose to regurgitation should the patient require general anesthesia. Similarly, the unpredictable efficacy and duration of action of antacids in many of the other patients suggest that the use of antacids during labor is not a reliable means of maintaining a high intragastric pH at this time, and thus additional antacid must be administered before induction of anesthesia. Because the repeated administration of antacids does not produce a more prolonged clinical effect (13) and, in the case of calcium-containing antacids, will even produce a rebound hypersecretion (30), there is little evidence to support the universal use of regular doses of antacids throughout labor. When antacids are administered as prophylaxis before general anesthesia, they should be given immediately before induction of anesthesia.

The present study indicates that studies assessing oral prophylaxis against acid aspiration should consider concomitant events that may alter gastric motility. Such variables must be controlled for valid conclusions about antacid effect. The action of the analgesics used during labor are especially important. Given the large number of possible interactions and the interpatient variability, patient safety from antacids can never be absolutely guaranteed. This strongly argues for clinical research into alternative methods of prophylaxis against the inhalation of gastric contents.

The help and cooperation of the patients and staff of the John Radcliffe Hospital are greatly appreciated.

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Effect of Left-to-Right, Mixed Left-to-Right, and Right-to-Left Shunts on Inhalational Anesthetic Induction in Children:

A Computer Model

Guy E. Tanner, MD, Denise G. Angers, MD, Paul G. Barash, MD, Adil Mulla, MD, Perry L. Miller, MD, PhD, and Peter Rothstein, MD

TANNER GE, ANGERS DG, BARASH PG, MULLA A, MILLER PL, ROTHSTEIN P. Effects of left-to-right, mixed left-to-right, and right-to-left shunts on inhalational anesthetic induction in children: a computer model. Anesth Analg 1985;64:101–7.

We describe a seven-compartment physiologic model of inhalational anesthetic induction with circulatory shunts that was used to simulate inhalational anesthetic induction in children with congenital heart disease. Our conclusions based on this model are that left-to-right (L–R) shunting has little effect on speed of induction; right-to-left (R–L) shunting significantly slows induction of N_2O and halothane anesthesia; and adding an L–R shunt to a preexisting R–L shunt will attenuate the slowing of induction caused by the R–L shunt.

Key Words: PHARMACOKINETICS—circulatory shunts. ANESTHESIA, CARDIOVASCULAR. HEART—congenital defects.

Controversy exists over the impact of left-to-right (L–R) shunts and mixed left-to-right and right-to-left (R–L) shunts (mixed shunts) on the rate of inhalational anesthetic induction in children with congenital heart disease (1,2). Data are lacking on the effect of L–R shunts and mixed shunts on inhalational anesthetic induction in these patients. No physiologic pharmacokinetic model has specifically addressed this question.

Physiologic pharmacokinetic modeling has proven valuable in understanding the kinetics of inhalational anesthetics. There are several reasons for this: protein binding and plasma pH apparently do not influence the distribution of these drugs; data on gas–blood and tissue–blood partition coefficients for many of these drugs are available in the literature; and, these drugs depend primarily on ventilation for their clearance. This means the differences in drug metabolism, protein binding, liver and kidney blood flow, or function, have little effect on steady-state anesthetic concentration. For these reasons, many of our concepts of anesthetic uptake and distribution have come from physiologic models by Eger, Mapleson, and others (3–10).

The purpose of our study was to create a computer model to explore the effects of L–R shunts and mixed shunts on the speed of inhalational anesthetic induction in children. The speed of inhalational anesthetic induction is determined by how rapidly adequate partial pressures of anesthetic are reached in the brain. Because the brain equilibrates rapidly with arterial blood, one way of comparing speed of inhalational induction in different circumstances is comparing rate of rise of arterial anesthetic partial pressures. In this paper, speed of induction refers to rate of rise of arterial anesthetic partial pressures. Because this rate changes with time, we chose to use graphic comparisons.

Methods

The model we designed consists of seven compartments. One compartment was used to represent each of the four tissue compartments used by Eger: vessel rich group (VRG), muscle, fat, and vessel poor group (VPG) (4). The heart was represented by two compartments, one for the right side and one for the left side. In addition, one compartment represented lung gas (functional residual capacity), lung tissue, and lung blood.

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Address correspondence to Dr. Tanner, Department of Anesthesiology, Veterans Administration Medical Center, West Spring Street, West Haven, CT 06516.

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Table 1. List of Variables Used in the Model

Symbol	Variable	Constant value
P_I	Inspired partial pressure	
P_A	Alveolar partial pressure	
P_a	Arterial blood partial pressure	
$P_{\bar{v}}$	Mixed venous blood partial pressure	
P_{vrg}	Vessel-rich group partial pressure	
P_{mus}	Muscle partial pressure	
P_{fat}	Fat partial pressure	
P_{vpg}	Vessel-poor group partial pressure	
$\dot{V}_A$	Alveolar minute ventilation	2.25 L/min
$\dot{Q}_{bc}$	Blood flow that perfuses body compartments (systemic cardiac output)	3.00 L/min
$\dot{Q}_P$	Pulmonary blood flow that engages in gas exchange	
$\dot{Q}_s$	R–L shunted blood	0.16 L/min
$\dot{Q}_{lr}$	L–R shunted blood	0.16 L/min
$\dot{Q}_t$	Total cardiac output ($\dot{Q}_{bc}$ + $\dot{Q}_{lr}$)	3.16 L/min
f_{vrg}	Fraction systemic blood flow to vessel-rich group	0.75
f_{mus}	Fraction system blood flow to muscle	0.18
f_{fat}	Fraction system blood flow to fat	0.054
f_{vpg}	Fraction system blood flow to vessel-poor group	0.016
Wt	Body weight	25 kg
FRC	Alveolar gas volume	0.821 L
V_{lt}	Lung tissue volume	0.286 L
V_{lb}	Lung blood volume (0.071 × $\dot{Q}_t/\dot{Q}_s$ L)	
V_{rtht}	Right heart volume	0.040 L
V_{ltht}	Left heart volume	0.040 L
V_{vrg}	Vessel rich group volume	2.25 L
V_{mus}	Muscle volume	12.5 L
V_{fat}	Fat volume	5.0 L
V_{vpg}	Vessel-poor group volume	5.25 L
λ_{bg}	Blood–gas partition coefficient	
λ_{vrg}	Vessel-rich group blood partition coefficient	
λ_{mus}	Muscle–blood partition coefficient	
λ_{fat}	Fat–blood partition coefficient	
λ_{vpg}	Vessel-poor group–blood partition coefficient	
λ_{lt}	Lung tissue–gas partition coefficient	

The circulation was represented as follows: venous blood returning from body tissue compartments and L–R shunted blood mixed in the right side of the heart, and pulmonary blood that had equilibrated with lung gas and R–L shunted blood mixed in the left side of the heart. To simulate circulation time, delays were added between the left side of the heart and body tissue compartments and between body tissue compartments and the right side of the heart. Two additional relationships were added to make the model more realistic. First, the concentration effect was modeled for N_2O by increasing ventilatory inflow to compensate for gas uptake. Second, lung blood volume was related to pulmonary blood flow in L–R shunting. Although other experimentally determined relationships between anesthetic depth and ventilation or cardiac output could have been incorporated into this model, these relationships were omitted so that the effects of L–R shunts and mixed shunts would be clear.

Four constraints were used in this simulation. First, ventilation and circulation were represented as smooth continuous processes. Although these are really pulsatile processes, approximating them as continuous processes simplifies the model. This simplification is frequently used in modeling uptake and distribution of inhalational anesthetics, and does not introduce significant errors (10–12). Second, cardiac output, shunt fraction, and regional blood flow were maintained constant during each simulated induction. Third, ventilation was constant except for simulations of nitrous oxide induction where it was increased to compensate for gas uptake (concentration effect). Fourth, anesthetic metabolism was considered negligible.

We modeled three anesthetics: N_2O, halothane, and diethyl ether. These were chosen because they represent anesthetics of low, medium, and high solubility. Shunt-induced changes in speed of induction were compared to the model's "normal" 7-yr-old child, whose physiologic characteristics were defined as follows: weight, 25 kg; body surface area, 1.0 m^2; alveolar minute ventilation ($\dot{V}_A$) 2.25 L/min; total cardiac output ($\dot{Q}_t$), 3.16 L/min; physiologic R–L shunt 0.05%, (0.16 L/min); physiologic L–R shunt 0.05%, (0.16 L/min).

Table 2. Rate Equations that Describe the Anesthetic Partial Pressure Relationships between Compartments

$$dP_A/dt = (\dot{V}_A\,(P_I - P_A) - \lambda_{bg}\dot{Q}_p\,(P_A - P_{\bar{v}}))/(FRC + \lambda_{lt}V_{lt} + \lambda_{bg}V_{lb})$$

$$dP_{\bar{v}}/dt = (f_{vrg}\dot{Q}_{bc}P_{vrg} + f_{mus}\dot{Q}_{bc}P_{mus} + f_{fat}\dot{Q}_{bc}P_{fat} + f_{vpg}\dot{Q}_{bc}P_{vpg} + \dot{Q}_{lr}P_a - \dot{Q}_tP_{\bar{v}})/V_{rtht}$$

$$dP_a/dt = (\dot{Q}_pP_A + \dot{Q}_sP_{\bar{v}} - \dot{Q}_tP_a)/V_{ltht}$$

$$dP_{vrg}/dt = f_{vrg}\dot{Q}_{bc}\,(P_a - P_{vrg})/(\lambda_{vrg}V_{vrg})$$

$$dP_{mus}/dt = f_{mus}\dot{Q}_{bc}\,(P_a - P_{mus})/(\lambda_{mus}V_{mus})$$

$$dP_{fat}/dt = f_{fat}\dot{Q}_{bc}\,(P_a - P_{fat})/(\lambda_{fat}V_{fat})$$

$$dP_{vpg}/dt = f_{vpg}\dot{Q}_{bc}\,(P_a - P_{vpg})/(\lambda_{vpg}V_{vpg})$$

These equations do not include circulatory delays and the concentration effect for N_2O. They were omitted to simplify understanding of the essential relationships.

The distribution of blood flow perfusing body compartments ($\dot{Q}_{bc}$) was as follows: 75% of $\dot{Q}_{bc}$ perfuses VRG; 18% of $\dot{Q}_{bc}$ perfuses muscle; 5.4% of $\dot{Q}_{bc}$ perfuses fat; and 1.6% of $\dot{Q}_{bc}$ perfuses VPG. Functional residual capacity (FRC) was 0.821 L. The differential equations defining the model can be found in Tables 1 and 2. The model was integrated using the Dynamo modeling language on an IBM 370 mainframe computer.

Results

L–R shunts

For L–R shunts without coexisting significant R–L shunts, two results were obtained. First, if systemic blood flow remained normal ($\dot{Q}_{bc}$ = 3.0), no significant change was seen in the speed of induction. This is shown in Figure 1. Here, arterial-to-inspired concentration ratio for N_2O is plotted vs time. In this figure, the solid curve represents the previously defined control, and the dashed curve represents an L–R shunt with a total-to-systemic blood flow ratio ($\dot{Q}_t/\dot{Q}_{bc}$) of 2. The reason for the small difference is that the control includes a physiologic 5% R–L shunt. (As will be discussed later, adding an L–R shunt to an R–L shunt results in a faster induction).

Second, if systemic blood flow is decreased from normal levels and the distribution of blood flow remains normal; then induction is slower in the first few minutes but then faster. The difference, however, is small. This is shown in Figure 2. VRG-to-inspired concentration ratio for N_2O is plotted vs time. The solid curve again represents control. The dashed curve represents a large L–R shunt ($\dot{Q}_t/\dot{Q}_{bc}$ = 4) with a 30% reduction in tissue perfusion. Although this presumes a reduction in cerebral blood flow, that flow is still 93 ml/100 g of brain tissue (normal $\dot{Q}_t$ in children is higher than adults when compared to body weight). For anesthetics more soluble than N_2O, changes in speed of induction are smaller.

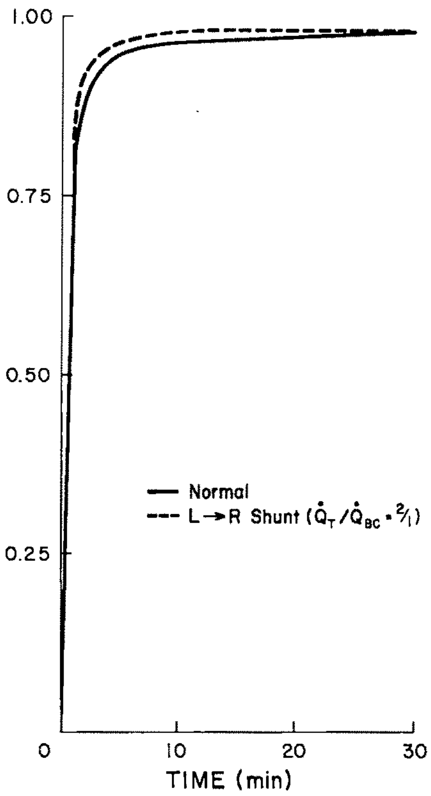

Figure 1. Arterial-to-inspired concentration ratio for N_2O modeled with and without a moderate L–R shunt and normal tissue perfusion. For the normal simulation, $\dot{Q}_{bc}$ = 3.0 L/min, $\dot{Q}_t$ = 3.16 L/min, $\dot{Q}_{lr}$ = 0.16 L/min, and $\dot{Q}_s$ = 0.16 L/min. For the L–R shunt simulation, $\dot{Q}_{bc}$ = 3.0 L/min, $\dot{Q}_t$ = 6.0 L/min, $\dot{Q}_{lr}$ = 3.0 L/min, and $\dot{Q}_s$ = 0.3 L/min.

R–L shunts

For R–L shunts without coexisting L–R shunting, two results were obtained. First, induction is slowed with all three anesthetics modeled. And second, the impact of a R–L shunt on the speed of inhalational induction is greater with anesthetics of lower solubility. These results are shown in Figure 3. Here, the difference between arterial anesthetic concentration with and without a 50% R–L shunt is plotted as a function of time. As can be seen, the greatest initial change occurs with N_2O. Figure 4 shows the effects of a 20% R–L shunt. Again, greater slowing of induction is seen with anesthetics of lower solubility; however, changes are modest with all anesthetics.

Mixed Shunts

Our simulations suggest that mixed shunts cause less slowing of inhalational induction than predominantly R–L shunts. Mixed shunts occur, for instance, in some cases of ventricular septal defects and in children with Tetralogy of Fallot who have had a Blalock–Tausig

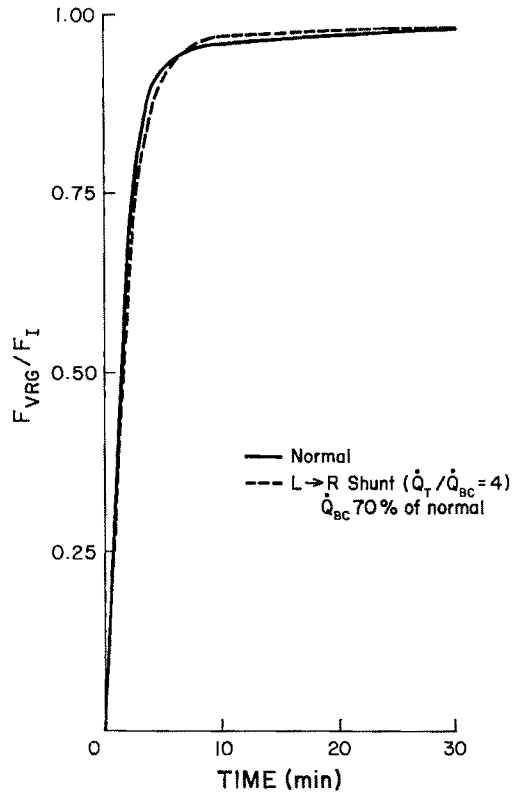

Figure 2. VRG-to-inspired concentration ratio for N_2O modeled with and without a large L–R shunt and reduced tissue blood flow. For the normal simulation, $\dot{Q}_{bc}$ = 3.0 L/min, $\dot{Q}_t$ = 3.16 L/min, $\dot{Q}_{lr}$ = 0.16 L/min, and $\dot{Q}_s$ = 0.16 L/min. For the L–R shunt simulation, $\dot{Q}_{bc}$ = 2.1 L/min, $\dot{Q}_t$ = 8.4 L/min, $\dot{Q}_{lr}$ = 6.3 L/min, and $\dot{Q}_s$ = 0.42 L/min.

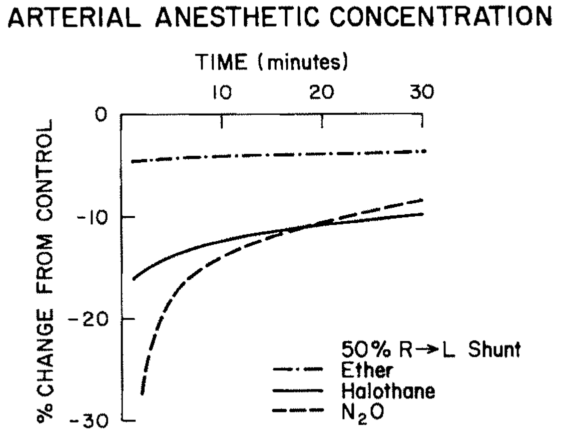

Figure 3. Decrease in arterial-to-inspired concentration ratio for three modeled anesthetics caused by a 50% R–L shunt. $\dot{Q}_{bc}$ = 3.0 L/min, $\dot{Q}_t$ = 3.16 L/min, $\dot{Q}_{lr}$ = 0.16 L/min, and $\dot{Q}_s$ = 1.58 L/min.

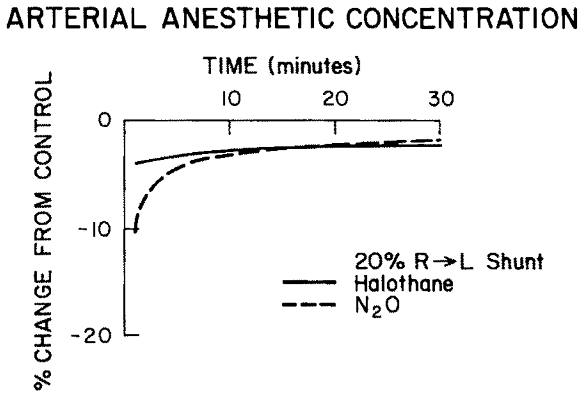

Figure 4. Decrease in arterial-to-inspired concentration ratio for two modeled anesthetics caused by a 20% R–L shunt. $\dot{Q}_{bc}$ = 3.0 L/min, $\dot{Q}_t$ = 3.16 L/min, $\dot{Q}_{lr}$ = 0.16 L/min, and $\dot{Q}_s$ = 0.63 L/min.

procedure (which creates an L–R shunt). This point will be illustrated with two cases, one hypothetical and one actual.

For the first case, the model's hypothetical 7-yr-old, 25 kg child was given a 50% R–L shunt. To this 50% R–L shunt, a 50% L–R shunt was added. This is shown in Figure 5. Here again the solid line represents arterial anesthetic partial pressures seen with only physiologic shunting (normal). The dotted curve represents arterial anesthetic partial pressures in a 50% R–L shunt. The dashed curve represents a mixed 50% R–L and 50% L–R shunt. As can be seen, adding an L–R shunt to a large R–L shunt results in a significantly faster induction.

For the second case, catheterization data from a child with pulmonary atresia and VSD were used. This child previously had both Waterston–Cooley and Blalock–Tausig shunts created. The catheterization showed a systemic blood flow ($\dot{Q}_{bc}$) of 4.4 L·min^{-1}·m^{-2}, an L–R shunt ($\dot{Q}_{lr}$) of 3.0 L·min^{-1}·m^{-2}, and an R–L shunt ($\dot{Q}_s$) of 1.9 L·min^{-1}·m^{-2}.

His body weight, cardiac output, and shunt fractions were entered into the model. An N_2O induction was simulated without and then with the surgically created L–R shunts. This is shown in Figure 6. Here, the solid curve depicts what the situation would be without L–R shunting, and the dashed curve depicts the patient's situation with mixed shunts. Addition of L–R shunts in this child should lead to a faster induction.

Discussion

The speed of an inhalational anesthetic induction is determined by how fast an anesthetizing pressure is reached in the brain. This in turn is determined by three rates: rate of anesthetic inflow into the lungs; rate of anesthetic transfer from the lungs to arterial blood; and rate of anesthetic transfer from arterial blood to brain.

An R–L shunt will slow induction. This is because

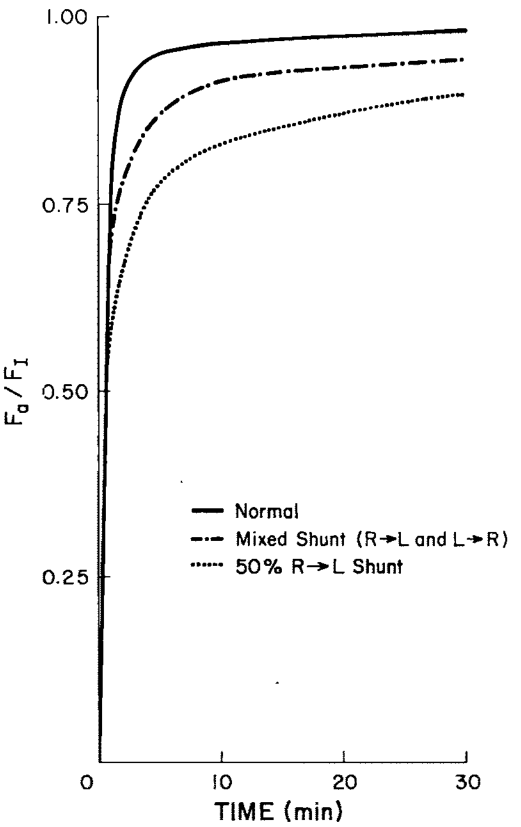

Figure 5. Arterial-to-inspired concentration ratio for N_2O modeled with R–L shunting, mixed shunting, and without shunting (normal). For the normal simulation, $\dot{Q}_{bc} = 3.0$ L/min, $\dot{Q}_t = 3.16$ L/min, $\dot{Q}_{lr} = 0.16$ L/min, and $\dot{Q}_s = 0.16$ L/min. For the R–L shunt simulation, $\dot{Q}_{bc} = 3.0$ L/min, $\dot{Q}_t = 3.16$ L/min, $\dot{Q}_{lr} = 0.16$ L/min, and $\dot{Q}_s = 1.58$ L/min. For the mixed shunt simulation, $\dot{Q}_{bc} = 3.0$ L/min, $\dot{Q}_t = 6.0$ L/min, $\dot{Q}_{lr} = 3.0$ L/min, and $\dot{Q}_s = 3.0$ L/min.

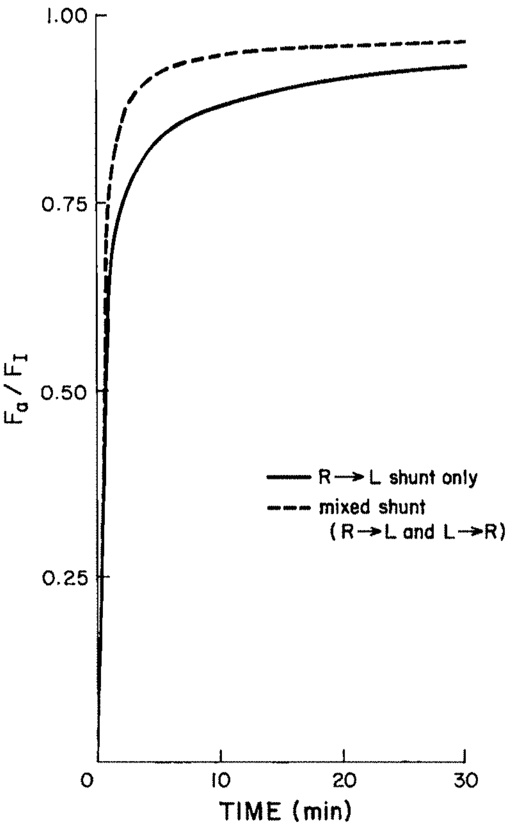

Figure 6. Simulated N_2O arterial-to-inspired concentration ratio for a child with pulmonary atresia and a VSD with surgically created L–R shunting. For the R–L shunt only simulation, $\dot{Q}_{bc} = 4.4$ L/min/m², $\dot{Q}_t = 4.62$ L/min/m², $\dot{Q}_{lr} = 0.22$ L/min/m², and $\dot{Q}_s = 1.9$ L/min/m². For the mixed shunt simulation, $\dot{Q}_{bc} = 4.4$ L/min/m², $\dot{Q}_t = 7.4$ L/min/m², $\dot{Q}_{lr} = 3.0$ L/min/m², and $\dot{Q}_s = 1.9$ L/min/m².

less anesthetic is absorbed from the lung. Less anesthetic is therefore available for the brain. Thus a slower induction is seen. The magnitude of the change depends on the anesthetic's solubility. To understand this, consider the induction of ether anesthesia. At the start of anesthesia (that is at $t = 0$), if the alveolar minute ventilation is 3 L/min, inhalation of 10% ether will deliver 300 ml/min of ether to the lungs. However, with a blood–gas partition coefficient of 13, and a cardiac output of 3 L/min, the blood could carry away 3900 ml/min, if ventilatory inflow were unlimited. Thus the induction of a highly soluble anesthetic-like ether is limited by ventilation. An R–L shunt will decrease the rate of absorption from the lung, but this is not the rate-limiting step. Contrast this with the situation with N_2O. With that same 3 L/min alveolar minute ventilation, and 3 L/min cardiac output, inhalation of 70% N_2O will deliver N_2O to the lungs at a rate of 2100 ml/min. But with a blood–gas partition coefficient of 0.47, the maximum rate of absorption is 987 ml/min. Thus an R–L shunt, which decreases effective pulmonary blood flow, will have a significant effect on induction.

An L–R shunt increases effective pulmonary blood flow. When combined with a physiologic (5%) R–L shunt, the increased pulmonary blood flow does not result in a significantly higher arterial anesthetic concentration. If systemic blood flow remains normal, the rate of transfer of anesthetic to the brain is unchanged. Thus speed of induction is not increased. An L–R shunt can speed induction only if it results in a decreased cardiac output and an increased proportion of that reduced cardiac output goes to the brain.

Mixed shunting results in a more normal speed of induction than does pure R–L shunting. Following the above reasoning, this is more easily understood. An R–L shunt decreases effective pulmonary blood flow. For less soluble anesthetics, this will slow induction. Adding an L–R shunt to that R–L shunt will increase effective pulmonary blood flow and counteract the effect of the R–L shunt.

The effect of anesthetic level on cardiac output,

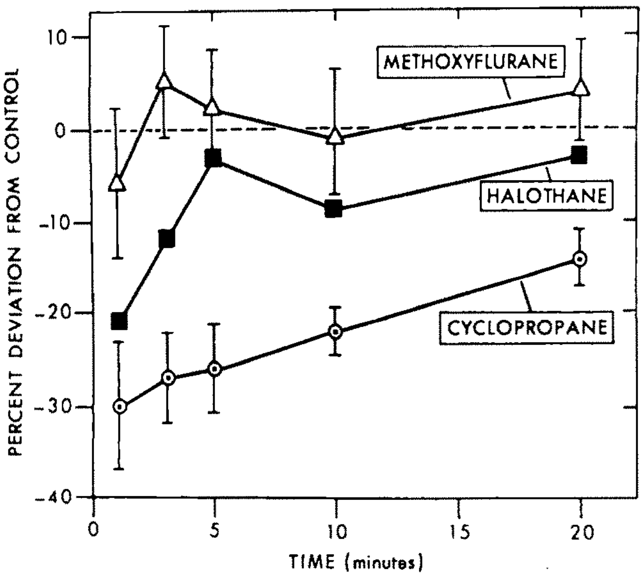

Figure 7. Measured change in arterial anesthetic concentration in the dog with ventilation blocked to one lung (from Stoelting and Longnecker (13) used with permission).

regional blood flow, and shunt fraction were not included in the simulations. The primary reason for omitting these relationships was lack of data to quantitate them. We speculate that an anesthetic-induced reduction in cardiac output with an increased fraction of cardiac output going to highly perfused tissues speeds induction. Also, with mixed shunting it is likely that anesthetics will increase right-sided pressures and decrease arterial pressure, thus causing an increase in R–L shunting and a decrease in L–R shunting. The impact of these changes in shunting would be a slower induction.

There is experimental verification for some of the conclusions reached by our computer model. Stoelting and Longnecker studied uptake of methoxyflurane, halothane, and cyclopropane in dogs with ventilation blocked to one lung (13). With one lung perfused, but not ventilated, a large R–L shunt would be expected. Their results are shown in Figure 7. Here percent change from control arterial anesthetic concentration is plotted vs time. As can be seen, the greatest change is seen with the least soluble anesthetic. Also, their experimental results are quite similar to the model's predicted results that were shown in Figure 4.

To our knowledge, there are no experimental data in animals or humans on anesthetic induction with L–R or mixed shunts. One could measure anesthetic uptake in animals before and after the surgical creation of shunts. Here, each animal could serve as its own control. The feasibility of obtaining data in humans is less promising. Adequate numbers of patients with shunts might be hard to find. Also, because these patients would be of different ages and sizes, matching study patients to controls would be a problem. All studies would require the measurement of arterial anesthetic partial pressures. In small patients (or small experimental animals) the amount of blood required to determine the anesthetic rate of rise could be large in comparison to the animal's blood volume. Also, because a 30% variation in alveolar anesthetic partial pressures is seen in normal subjects, the differences in rate of induction predicted by our simulations would be difficult to quantitate in patients (14).

In summary, we describe a seven-compartment mathematical model of inhalational anesthetic induction in children with congenital heart disease. It led us to the following conclusions: L–R shunts do not significantly speed inhalational induction; R–L shunts do slow induction of poorly soluble gases; and mixed shunts cause less slowing than predominantly R–L shunts.

The model is useful in understanding the kinetics of inhalational anesthetic induction in children with congenital heart disease. Also, it delineates problems of research in this area.

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Anesthesia for Hepatic Transplantation:
Cardiovascular and Metabolic Alterations and their Management

F.J. Carmichael, PhD, MD, FRCP(C), M.J. Lindop, MB, BChir, FFARCS, and
J.V. Farman, MB, BS, FFARCS

CARMICHAEL FJ, LINDOP MJ, FARMAN JV. Anesthesia for hepatic transplantation: cardiovascular and metabolic alterations and their management. Anesth Analg 1985;64:108–16.

We studied the cardiovascular and metabolic changes occurring during orthotopic liver transplantation in nine patients. The operative management of these patients can be divided into an initial dissection phase, an anhepatic phase when the hepatic artery, portal vein, and inferior vena cava are cross-clamped, and the phase after the release of these clamps. On clamping the inferior vena cava, the systolic arterial pressure decreased from 134 ± 9 to 104 ± 8 mm Hg, the pulmonary artery pressure decreased from 25 ± 4 to 17 ± 4 mm Hg, the mean pulmonary wedge pressure decreased from 11.9 ± 1.9 to 6.8 ± 1.2 mm Hg, and cardiac index decreased from 5.3 ± 0.3 to 2.7 ± 0.2 $L \cdot min^{-1} \cdot m^{-2}$. There were compensatory increases in systemic vascular resistance from 806 ± 52 to 1448 ± 109 $dyne \cdot cm \cdot sec^{-5}$ and in pulmonary vascular resistance from 78 ± 13 to 122 ± 25 $dyne \cdot cm \cdot sec^{-5}$. Removal of these clamps was followed by an initial depression in cardiac output that returned to preclamping values. Profound metabolic alterations were encountered during these phases. Hydrogen ion concentration increased from a mean of 39 ± 2 to 45 ± 2 nmol/L during cross-clamping, with a further increase to 55 ± 3 nmol/L after the initial perfusion of the new liver. Serum potassium levels increased significantly only on release of the clamps, from a mean of 3.8 ± 0.3 to a peak of 5.3 ± 0.6 mmol. With the reduction in pulmonary blood flow during the period of caval clamping, the end-tidal arterial carbon dioxide difference increased. These changes were independent of minute ventilation and returned to control levels by the end of the procedure. Blood glucose levels increased throughout initial stages of the operation from 12 ± 2 to 26 ± 3 mmol/L, but decreased by the end of surgery to 22 ± 2 mmol/L. These changes were due to a combination of hemodynamic effects of inferior cava clamping and the biochemical consequence of the introduction of the preserved liver into the circulation.

Key Words: LIVER—transplantation. ANESTHETIC TECHNIQUES—liver transplantation.

There have been more than 600 recipients for orthotopic liver transplantation worldwide (1). The indications for operation, medical considerations, and surgical procedures have been described (2,3). This procedure is arguably the most challenging ever regularly encountered by the anesthesiologist. Previous anesthetic reports from centers engaged in liver transplantation have outlined the problems encountered during this procedure (4–8). The patient's hepatic function is likely to be greatly compromised preoperatively, resulting in hemodynamic, hematologic, and metabolic abnormalities that must be optimized before surgery and compensated for during the anesthetic. During the operation there is a period of sudden and prolonged reduction in venous return to the heart while the vena cava is cross-clamped. This often occurs at a time of heavy blood loss. Finally, gross metabolic alterations commonly occur during the procedure as a result of the preexisting hepatic dysfunction, a 40–65 min anhepatic period, and as a result of the preservation of the donor liver, and compensation must be made for these.

In this paper, new data utilizing pulmonary artery catheters describe in more detail the cardiovascular and metabolic alterations encountered during nine orthotopic liver transplant operations conducted at Addenbrooke's Hospital in Cambridge, England. The current management of these conditions is discussed also.

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Address correspondence to Dr. Carmichael, Department of Anaesthesia, Toronto Western Hospital, 399 Bathurst Street, Toronto, ON, Canada M5T 2S8.

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Table 1. Patient Characteristics

Age (yr)	Diagnosis[a]	Bilirubin (μmol/L)	Protein total/ albumin (g/L)	Operative risk score[b]	Hb (g/dl)	Duration of surgery (hr)	Anhepatic period (min)	Blood loss (ml)
53	PBC	668	78/18	12	10.6	6.5	65	3000
57	PBC	368	69/17	11	12.7	6.0	40	3650
38	CAH	34	79/28	8	12.5	6.8	64	4500
42	PBC	384	63/26	12	11.9	6.0	50	6300
58	C-H	21	68/35	5	10.9	4.0	45	4480
23	CAH	87	56/22	14	11.9	9.0	48	11500
56	Hepatoma	10	73/23	8	14.4	6.5	39	8080
22	Hepatoma	9	72/46	5	14.6	4.3	43	1500
36	PBC	521	52/28	11	10.4	5.8	55	7240

Abbreviations:
[a]PBC, primary biliary cirrhosis; CAH, chronic active hepatitis; C-H, cirrhosis and hepatoma.
[b]Operative risk score from Pugh et al. (9).

Methods

Some salient features of each of the nine patients included in this study are given in Table 1. Their mean age was 43 ± 5 yr with a range of 22–58 yr. The bilirubin levels were markedly elevated in the patients with primary biliary cirrhosis (PBC) at 485 ± 70 mmol/L. All patients had hemoglobin levels above 10 g/dl. The white cell counts and platelet counts were in the normal range in all patients except number 6 who had a WBC of 2100 × 10^9/L and platelet count of 57 × 10^9/L. The mean operative risk score for patients with liver disease, as defined by Pugh et al. (9), of 9.4 ± 1.1 placed the nine patients in a poor risk category, while the severely cirrhotic patients had higher scores than the two noncirrhotic patients (11.3 ± 0.8 vs 5 and 5). The average duration of the anesthetic was 6.1 ± 0.5 hr, with the mean anhepatic phase lasting 50 ± 3 min. The average blood loss was 5.6 ± 1.0 L, which was replaced with whole blood. Four of the patients were female, each with PBC.

The various stages of the procedure were as follows. After induction of anesthesia and establishment of monitoring, which took about 30 min (A in the figures), the surgical procedure began (10). This involved an initial dissection phase (B in the figures) lasting 1–4.5 hr, during which the inferior vena cava (IVC) above and below the liver, the portal vein, the hepatic artery, and the common bile duct were isolated. With the cross-clamping of the hepatic artery, portal vein, suprahepatic cava (above the hepatic veins immediately below the diaphragm), and infrahepatic cava, the operation entered the anhepatic phase (C in the figures), lasting about 50 min. During this phase the recipient's liver was removed, the donor's liver introduced and the donor and recipient suprahepatic cavae anastomosed, followed by the portal vein anastomosis. The new liver was then flushed out with 500 ml of stored plasma protein solution through the portal vein and was allowed to drain via the temporarily unclamped infrahepatic cava. The portal vein and the suprahepatic cava next were unclamped, allowing the new liver to be perfused with the patient's blood and ending the anhepatic phase (D in the figures). The infrahepatic vena cava and the hepatic artery were then anastomosed, and after the release of their clamps (D′ in the figures), normal circulation was restored. Phase D and D′ together lasted 15–64 min. Subsequently the gall bladder was anastomosed over a period of 30 min (E), followed by skin closure (F). At the completion of the operation (G), the patient was transported to the intensive care unit.

The patients received an oral benzodiazepine premedication given 1.5 hr before going to the operating suite. The cirrhotic patients received 0.5–1.0 L of fresh frozen plasma prior to surgery. At induction, patients were given 100–200 μg of fentanyl, followed by 3–5 mg/kg of thiopental, and 1.5 mg/kg of succinylcholine prior to intubation with a soft-cuffed endotracheal tube. Anesthesia was maintained with 30–35% oxygen and 65–70% nitrous oxide throughout the procedure and a muscle relaxant, either pancuronium or alcuronium. Additional fentanyl and trichlorethylene, up to 0.5%, were added as required for analgesia. The minute ventilation was adjusted to produce a Pa_{CO_2} of 27–34 mm Hg.

Two 12-gauge intravenous lines were inserted to allow for the rapid administration of blood using Fenwal pressure infusion bags maintained at 300 mm Hg as previously described (8). Fluid management included 4% dextrose in 0.18% NaCl as a continuous intravenous infusion at 100–200 ml/hr and blood transfusion to replace measured loss and maintain cardiovascular stability. Whole blood containing CPD

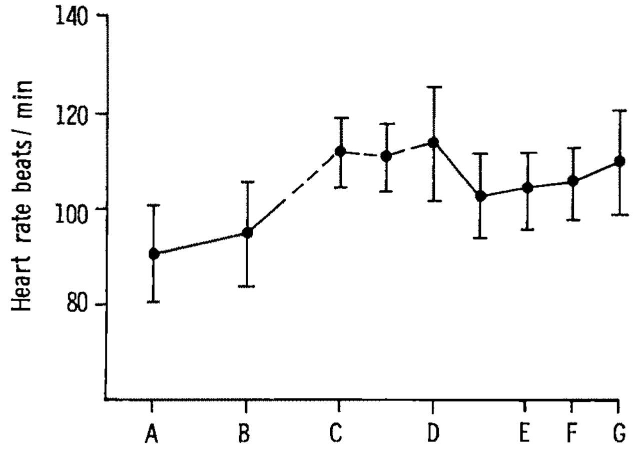

Figure 1. Changes in heart rate at the various phases during liver transplantation. Mean ± SEM for nine patients. Phase: A—induction, B—dissection, C—anhepatic, D—partial anhepatic, E—gall bladder anastomosis, F—skin closure, G—end of procedure. See text for details of A–G.

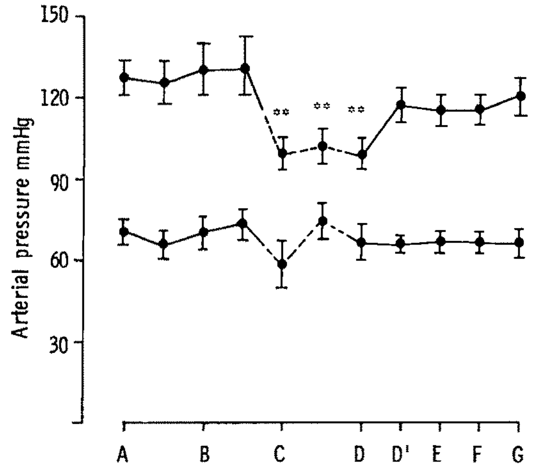

Figure 2. Changes in arterial systolic and diastolic pressure during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$.

anticoagulant solution with adenine was used, with every fifth to sixth unit transfused being fresh whole blood.

Cardiovascular function was monitored using an electrocardiogram (lead 1) and a radial artery catheter inserted by percutaneous puncture to monitor systemic arterial pressure. A Swan–Ganz type balloon-tipped pulmonary artery catheter was inserted via the right internal jugular vein under pressure monitoring for continuous monitoring of the central venous pressure (CVP) and pulmonary artery (PA) pressure, as well as intermittent measurement of the pulmonary wedge pressure (PWP) and cardiac output by thermal dilution, using a cardiac output computer. Records were made on a strip chart recorder. PWP, CVP, and cardiac output readings were taken in the expiratory phase of ventilation. Cardiac output determinations were obtained during periods of relative cardiovascular stability because rapid blood loss and transfusion may interfere with these determinations. An infrared carbon dioxide analyzer was used to monitor end-tidal carbon dioxide levels.

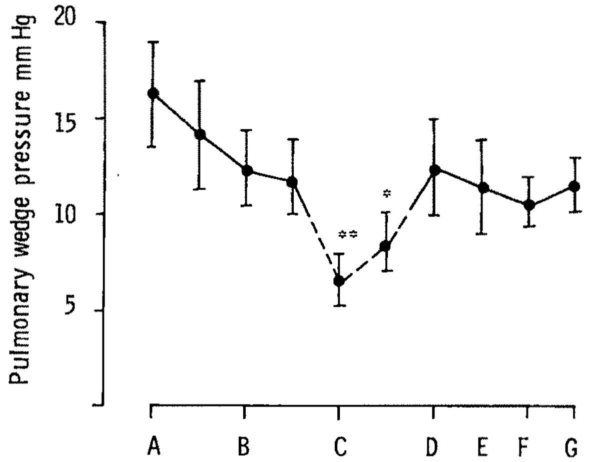

Figure 3. Changes in pulmonary wedge pressure during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$, $*P < 0.05$.

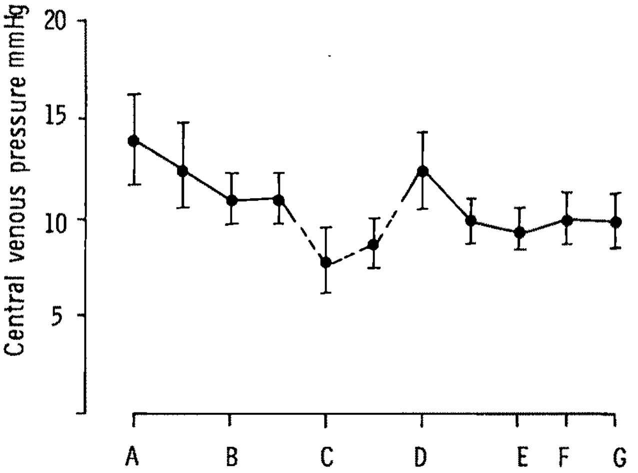

Figure 4. Changes in central venous pressure during liver transplantation. Mean ± SEM for nine patients.

Blood samples were drawn at intervals during the various phases of the procedure for measurement of serum electrolyte, blood sugar, and blood gas tensions (11). Toward the end of surgery, blood was also drawn for a coagulation screen and hemoglobin levels.

All data are presented as means ± SEM. Data were analyzed using an analysis of variance. Values obtained prior to cross-clamping were used as controls, unless otherwise stated. Statistical significance of differences between mean values was determined by the

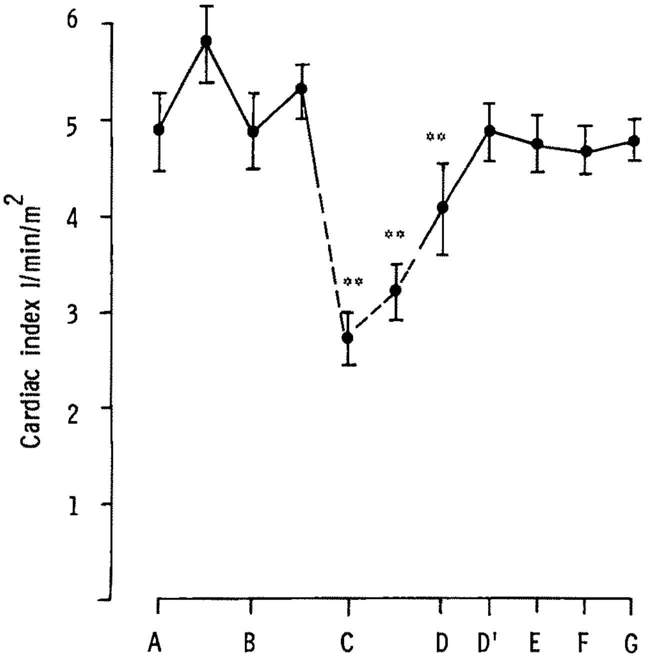

Figure 5. Changes in cardiac index during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$, $*P < 0.05$.

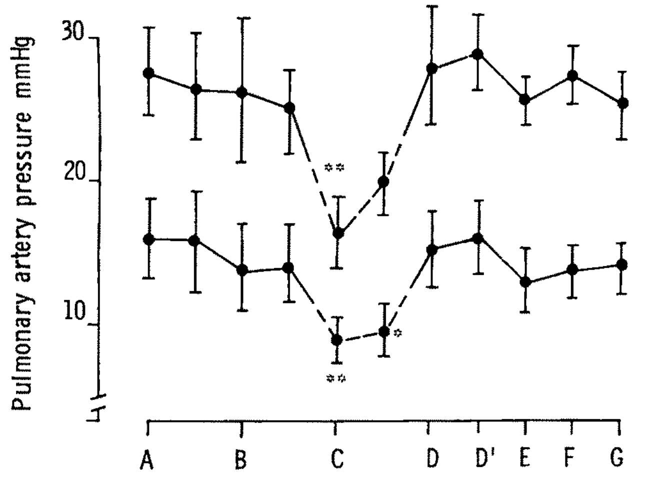

Figure 6. Changes in pulmonary arterial systolic and diastolic pressures during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$, $*P < 0.05$.

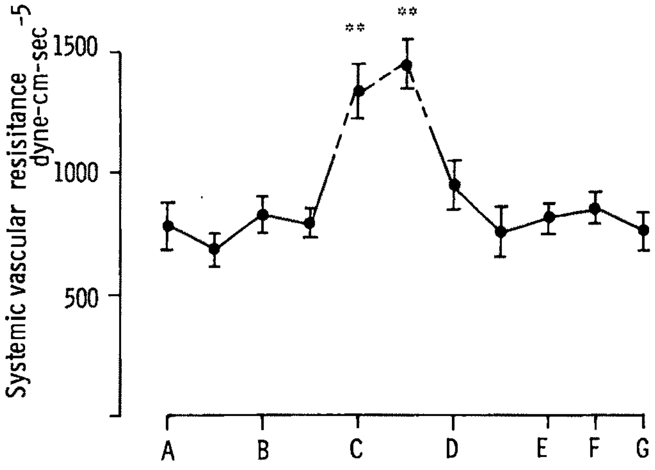

Figure 7. Changes in systemic vascular resistance during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$.

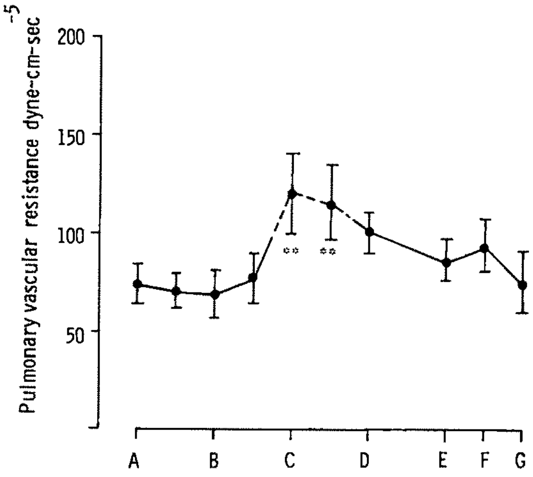

Figure 8. Changes in pulmonary vascular resistance during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$, $*P < 0.05$.

least significant difference method, using a pooled estimate of variance derived from the analysis of variance (12).

Results

The hemodynamic findings during liver transplantation in nine patients are presented in Figures 1–8. From induction (A) up to the cross-clamping of the IVC (C), the heart rate (Fig. 1), the arterial pressure (Fig. 2), PWP (Fig. 3), and CVP (Fig. 4) were within the normal range, although there was a gradual reduction in the PWP from 16.3 ± 2.7 to 11.9 ± 1.9 mm Hg and the CVP from 14.1 ± 2.2 to 10.8 ± 1.4 mm Hg. The cardiac index (Fig. 5), PA pressure (Fig. 6), systemic vascular resistance (SVR) (Fig. 7), and pulmonary vascular resistance (PVR) (Fig. 8) also remain relatively constant.

With cross-clamping of the IVC (point C) there was an immediate 24% decrease in the systolic arterial pressure and a small but not significant decrease in diastolic pressure below preclamping values. There were corresponding decreases in PWP (42%), CVP (26%), cardiac output (48%), and pulmonary artery systolic and diastolic pressures (each 36%). The SVR

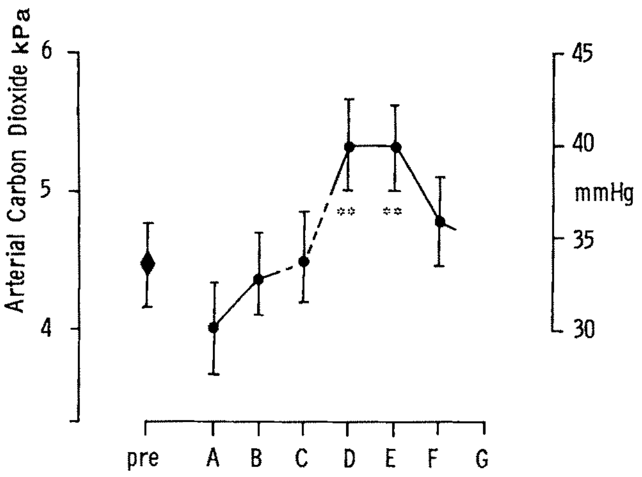

Figure 9. Changes in arterial carbon dioxide tensions during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$.

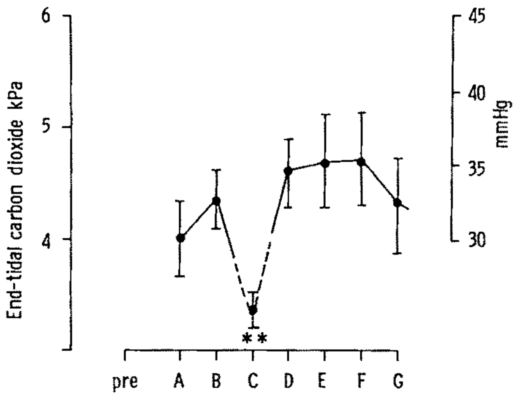

Figure 10. Changes in end-tidal carbon dioxide tensions during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$.

and PVR increased 66% and 44%, respectively, while the heart rate increased 17%.

With the simultaneous unclamping of the suprahepatic vena cava and portal vein (point D) there were increases in PWP and CVP to their preclamping levels, although the arterial pressures still remained depressed. At this time cardiac output increased slightly but still remained 27% below its preclamping value. Pulmonary artery systolic and diastolic pressures rose to their preclamping values, while SVR and PVR decreased towards control levels. All cardiovascular measurements subsequently returned to preclamping levels after unclamping of the infrahepatic cava and hepatic artery and were maintained at these levels, by transfusion of whole blood as necessary until the completion of the operation.

Metabolic changes during liver transplantation are shown in Figures 9–14. Patients exhibited a mild degree of respiratory alkalosis, with a $Paco_2$ ranging from 3.5 to 4.5 kPa (27–34 mm Hg) (Fig. 9), which remained relatively constant until the anhepatic phase (C). During the anhepatic phase there was a 20% decrease in end-tidal CO_2 (Fig. 10) from 4.3 ± 0.4 to 3.4 ± 0.3% kPa (32 ± 3 to 25 ± 2 mm Hg) with little initial change in $Paco_2$. After vascularization of the new liver (point D), the end-tidal CO_2 increased above the preclamping level to 4.8 ± 0.4 kPa (36 ± 3 mm Hg) and the $Paco_2$ increased to 5.3 ± 0.3 kPa (40 ± 2 mm Hg) (Fig. 9). These values gradually returned to preclamping levels by the end of operation. Arterial oxygenation remained at 17.4 ± 2.0 kPa (130 ± 15 mm Hg) throughout the procedure with an inspired oxygen concentration of 30–35%.

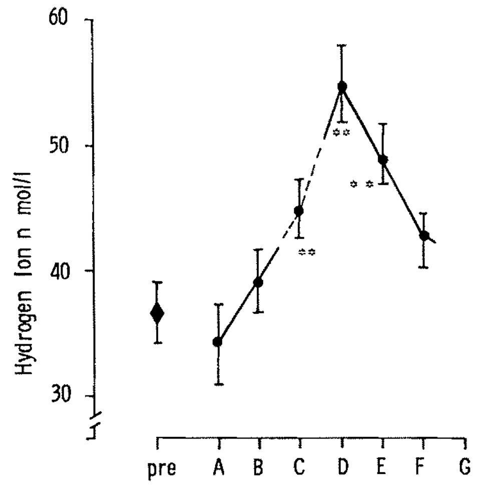

Figure 11. Changes in arterial plasma hydrogen ion concentrations during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$.

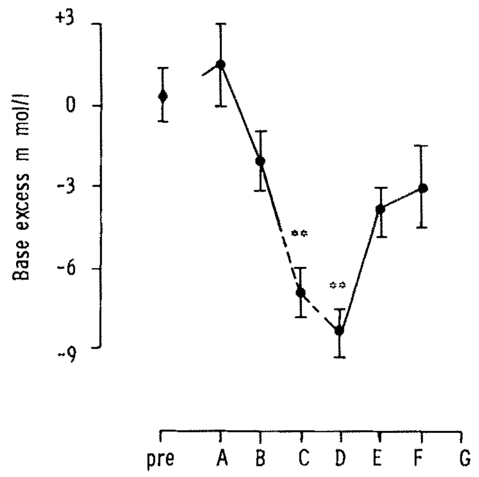

Figure 12. Changes in base deficit during liver transplantation. Mean ± SEM for nine patients. **Differences from preclamping values statistically significant $P < 0.01$.

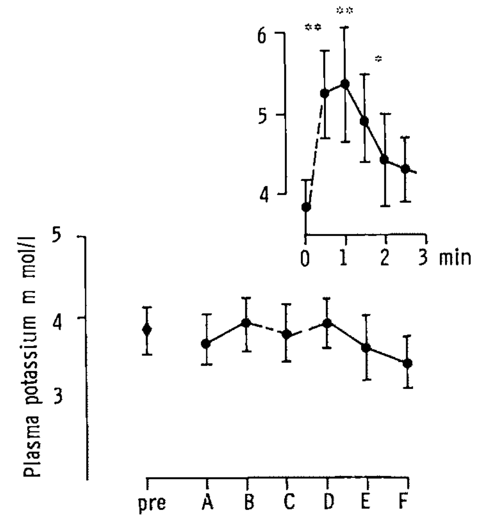

Figure 13. Changes in pulmonary arterial plasma potassium concentrations during liver transplantation. Mean ± SEM for nine patients. Inset: plasma potassium samples taken from the pulmonary artery catheter over 30-sec periods after the release of clamps from the portal vein and suprahepatic artery in eight patients. **Differences from preclamping values statistically significant $P < 0.01$, $^*P < 0.05$.

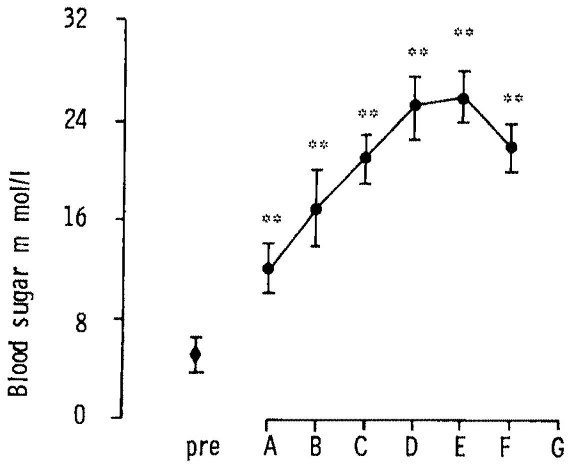

Figure 14. Changes in blood sugar concentrations during liver transplantation. Mean ± SEM for nine patients. **Differences from preoperative values statistically significant $P < 0.01$.

Patient temperatures decreased during the operation to 35.6 ± 0.4°C prior to cross-clamping of the hepatic vessels. There was a further decrease of about 1°C after the insertion of the cold donor liver that had been stored at 0–4°C. The body temperatures gradually increased to 35.8 ± 0.3°C by the end of the surgery (results not shown).

During the course of the surgery there was a gradual increase in hydrogen ion (H^+) concentration (Fig. 11) and in base deficit (Fig. 12), both of which became pronounced during the anhepatic phase (C). With revascularization of the new graft plus the reintroduction into the circulation of the blood held below the liver (D), there was a further increase in the serum H^+ that later gradually returned towards normal values. Changes in base excess mirror these changes in H^+ with the most dramatic alterations occurring at the time of unclamping of the suprahepatic vena cava.

Serum potassium levels remained relatively stable throughout the early part of the operation (Fig. 13). Although in some patients there was little elevation in potassium concentration, in the majority the revascularization of the new liver and release of the suprahepatic clamp (D) was followed by a dramatic but transient elevation, as shown in the inset to Figure 13. Each blood sample was drawn through the PA catheter over a period of 30 sec. The highest serum level measured was 7.8 mmol/L. After the introduction of the new liver into the circulation, there was a gradual decrease in potassium levels.

With the removal of the suprahepatic and portal vein clamps, there were dramatic reductions in heart rate along with multiple ventricular ectopic beats, elevated T-waves, and reductions in the size of the QRS complexes.

Blood glucose levels were normal in all recipients preoperatively (Fig. 14). During the anesthetic, including the anhepatic phase, there was a continual increase in glucose levels to a peak of 26.4 ± 2.1 mmol/L, followed by a small decline during the skin closure (F).

Discussion

The patients having orthotopic hepatic transplantation in this study were in poor physical condition, as reflected by the operative risk score (9), although those with hepatic tumors, patients 5 and 8, were in better general condition. The anesthetic technique and duration of surgery and anhepatic phase, as well as the operative blood loss and replacement were all similar to those described previously (4,5,8). However, use of pulmonary artery catheters allowed more detailed analysis of the cardiovascular alterations during this procedure, as well as a more detailed assessment of the changes in potassium levels occurring during the initial perfusion of the new liver. Because of the poor condition of most of the liver transplant patients and because of the large volumes of blood that can be lost and transfused, the use of pulmonary artery catheters is beneficial in the monitoring of these patients. In the present study the arterial pressures remained in the normal range throughout the operation. They were maintained primarily by transfusion of whole blood to replace surgical losses, which on occasion may be very large in this type of surgery, as much as 18 L (7) or more (13). The PWP and CVP started in the high normal range in the cirrhotic patients in this study because they were given 0.5–1.0 L of fresh frozen plasma before surgery in order to supply adequate levels of coagulation factors (14). These pressures gradually decreased, reflecting blood loss in excess of replacement. Pulmonary artery pressures also remained normal until the inferior vena cava was clamped.

Cardiac output has been shown to be high in patients with liver failure, reflecting the presence of vascular shunts (15,16). Cardiac index was also high in the present study in the initial phases of the operation with SVR in the lower normal range.

At the time of cross-clamping of the IVC (point C), prior to the removal of the old liver, there was a dramatic decrease in systolic arterial pressure similar to that previously reported (5,6). A trial or test clamping of the IVC is usually performed; a precipitous fall in arterial pressure suggests an inadequate circulating blood volume. The patient is then transfused with whole blood before proceeding with clamping of the IVC. In all the present cases, additional transfusions alone were adequate to maintain blood pressure, though in the past it has been necessary to use femoral artery–vein bypass to maintain adequate circulation (17).

Acute obstruction of the IVC is known to cause decreases in arterial pressure and cardiac output (18). Cross-clamping of the IVC would be expected to completely block venous return from below the diaphragm, except for that returning via the azygos system and collateral channels. Clamping of the IVC thus would be expected to result in a reduction by half in venous return to the heart. In the present study the 48% decrease in cardiac output with clamping of the IVC is in keeping with this prediction and was associated with 42 and 27% decreases in PWP and CVP, respectively. Because of the dramatic reduction in venous return, it would appear that the collateral circulation in our patients was not substantial. Although attempts to augment filling pressures by blood transfusion improved cardiac output, too rapid a transfusion rate tended to overload the heart, resulting in increased PA pressure and CVP without a corresponding increase in cardiac output and arterial pressure. There were compensatory elevations in heart rate (15%), SVR (66%), and PVR (44%). This is evidence of persistent sympathetic nervous system activity reflecting light levels of anesthesia (7).

As the venous return from below the diaphragm was restored (points D and D′ in the figures), the PWP and CVP returned to preclamping levels. One might expect the blood pressure and cardiac output similarly to return to preclamping levels as suggested by Scott (18); however, both of these values at first remained depressed after the clamps were removed (point D), possibly due to the metabolic alterations described below.

Plasma potassium values remained relatively constant throughout the procedure except for one critical period. With the introduction of the new liver into the circulation there was often a dramatic, albeit transient increase in plasma potassium levels (inset Fig. 13). Elevated potassium levels caused major alterations in the cardiogram; commonly elevated T-waves and arrhythmias were seen. The source of the potassium is the new liver, which has been stored in lactated Ringer's solution at 0–4°C for up to eight hours. During this time potassium leaks out of hepatic cells. In spite of prior flushings, the newly grafted liver with 500 ml of plasma protein solution, when the clamps were removed from the portal vein and suprahepatic cava, cold hyperkalemic blood will flow directly into the central circulation. Cardiac arrest has been reported at this stage (7), and although this did not occur in the present study, potassium levels as high as 7.8 mmol/L were measured in the pulmonary artery. The potassium is likely to be distributed and taken up by cells throughout the body with a return to normal levels in 10–15 min, as indeed was found in the present study. The gradual decrease in serum potassium seen after the anhepatic phase is most likely an indication of the functioning of the new liver replacing its lost stores of potassium.

Changes in ionized calcium levels during liver transplantation have recently been reported (24). Ionized calcium levels could not be determined during the present study. During periods of rapid transfusion, when a citrate load was given to the patients, and immediately after the anhepatic phase, when potassium levels were elevated, levels of ionized calcium would have been helpful in patient management.

The causes of the acid–base alterations observed in our patients were multifactorial. First, the patients were hyperventilated to a mild degree of respiratory alkalosis. Second, rapid transfusion of blood contributes acid metabolites to the patient and increases the base deficit (19). Third, cross-clamping of the IVC leads to stagnation of blood below the diaphragm, resulting in the conversion to anaerobic tissue metabolism with the production and release of lactic acid. Fourth, the absence of hepatic function and the initially poor function of the newly grafted liver result in greatly reduced metabolism of citrate, lactate, and other acids. Fifth, the decrease in blood pressure commencing with the cross-clamping of the IVC may lead to reduced perfusion of tissues above the diaphragm with consequent hypoxia and production of acid. Finally, the low body temperature previously noted during liver transplantation (5) would further slow hepatic metabolism. The danger of giving too much bicarbonate is that the patients may develop metabolic alkalosis towards the end of the operation and in the postoperative period. We therefore gave our patients bicarbonate during the anesthetic only when the base deficit exceeded 6–8 mmol/L. The citrate given with each transfusion would also contribute to postoperative alkalosis as the new liver commenced function.

Depression of cardiovascular function after the initial perfusion of the newly grafted liver (point D), in spite of the restoration of venous return, probably resulted from elevation of serum levels of potassium and hydrogen ions and perhaps other vasoactive agents released from hypoxic tissues. By point E all measured cardiovascular functions had returned to their initial values, supporting the view that it was the changes in levels of serum, potassium, and hydrogen ions, and possibly other substances that were responsible for the cardiovascular depression at point D.

There are complex changes in carbon dioxide (CO_2) homeostasis during liver transplantation. The patients were hyperventilated to a mild degree of alkalosis to provide in advance partial compensation for the impending metabolic acidosis. With a decrease in body temperature, there will be some decrease in the rate of CO_2 production. Rapid transfusion of blood also imposes an increased load of CO_2 to excrete (19), as was often noted on the expired CO_2 trace. A reduction in pulmonary gas exchange with arterial hypotension (20) may also have occurred in our patients. The decrease in end-tidal CO_2 and the increase in arterial–alveolar P_{CO_2} gradient that we observed with cross-clamping of the IVC (point C) was probably a reflection of reduced lung perfusion associated with the reduction in cardiac output, resulting both in an increased mismatch of ventilation and perfusion, and a diminution in systemic venous carbon dioxide transport to the lungs. As a consequence, a progressive buildup of the body's store of CO_2 occurred, evident at point D, from the increase in arterial CO_2 tension. As normal pulmonary hemodynamics were reinstated at D′ and E, an increased pulmonary excretion of carbon dioxide was noted, accompanied by a decrease in the arterial CO_2 tension. The unclamping of the infrahepatic cava, however, did not appear to cause any further increase in carbon dioxide excretion.

Blood sugar levels are known to rise during general anesthesia (21), particularly during infusions of dextrose (22). The capacity for gluconeogenesis in an end-stage cirrhotic liver or in a cold, newly transplanted liver presumably will be limited, and during the anhepatic phase hypoglycemia might be anticipated because the majority of glucose is normally metabolized in the liver. To prevent hypoglycemia, intravenous glucose solution was infused throughout the operation, with additional glucose being supplied by the anticoagulant solution transfused with the blood. The average rate of supply of glucose was about 143 mmol/hr. The steady increase in blood sugar levels seen during the operation and in particular during the anhepatic period in this (Fig. 14) as in other studies (8) is attributable to a failure to utilize the glucose supplied and may possibly reflect the inability of the body to increase insulin release during general anesthesia (23). During the operative period, no attempt was made to treat the elevated glucose levels or to limit the glucose load. As with serum potassium levels, the decrease in blood sugar at the end of the operation most likely represented the onset of function of the new liver.

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Anesthesia for Pediatric Orthotopic Liver Transplantation

Lawrence M. Borland, MD, Marenea Roule, CRNA, and D. Ryan Cook, MD

BORLAND LM, ROULE M, COOK DR. Anesthesia for pediatric orthotopic liver transplantation. Anesth Analg 1985;64:117–24.

The anesthetic management of 68 liver transplantations in 50 pediatric patients is described. The surgical technique is briefly reviewed. The selection of an anesthetic technique was not as important as management of numerous intraoperative problems. Citrate intoxication secondary to massive blood transfusion in the hypothermic anhepatic patient is a major problem, as are coagulation deficiencies. Hyperkalemic cardiac arrest, also a significant hazard, produced the only intraoperative death.

Key Words: LIVER—transplantation. ANESTHETIC TECHNIQUES—liver transplantation.

The first clinical orthotopic liver transplant was performed at the University of Colorado in 1963, but until recently this procedure remained experimental and received little physician support (1). Advances in anesthetic technique and the introduction of more effective immunosuppressive agents have, however, improved survival rates and stimulated renewed interest in liver transplantation on the part of the medical community. Whereas experience in pediatric transplantation was once limited by the small number of donors and the need for organs of specific size, effective organ procurement networks and the presence of strong lay support have increased the number of available donor organs (2,3). A statement of "clinical usefulness" released by the National Institutes of Health and a request from the President of the United States for organ donation have also heightened public awareness of liver transplantation (4,5).

From May 1981 to June 1983, 50 pediatric patients received 68 liver transplants at the Children's Hospital of Pittsburgh. We review our experience and outline principles for managing the care of these critically ill patients.

Patient Population

Sixty-eight liver transplants were performed on 50 patients. The patients ranged in age from 7 months to 17 years. Table 1 and Figure 1 summarize the patients' diagnoses and ages at time of transplantation. The population was divided into four groups for the analysis of our intraoperative clinical experience.

In group 1 (the obstructive diseases), congenital biliary atresia was the most common disease process preceding liver transplantation (22 patients). Byler's syndrome (familial intrahepatic cholestasis with hypercholesterolemia progressing to early childhood cirrhosis) was the reason for transplantation in three cases. Alagille's syndrome or arteriohepatic dysplasia with decreased number of bile ducts within the portal tracts was the reason in another three cases. In group 2, terminal liver failure as a result of α-1-antitrypsin deficiency dysfunction ZZ genotype accounted for 10 transplantations. In group 3, failed liver transplants accounted for 18 of the transplants performed. The number of days from original transplant to repeat operation is noted in Table 1. Of this group, 12 patients had 2 transplants; 3 patients had 3. Group 4 includes various metabolic and infectious processes that produced hepatic failure. The etiology of hepatic failure in the 12 patients in this category ranged from neonatal hepatitis to glycogen storage disease type I (Table 2).

Surgical Technique

Liver transplantation is accomplished through a wide bilateral subcostal incision in the recipient with cephalad extension to the xyphoid. The xyphoid process is removed without entering the thorax. The liver is then freed up to its vascular pedicle (stage 1). Previous intraabdominal surgery (usually the Kasai procedure performed on patients with extrahepatic biliary atresia) contributed to adhesions and subsequent increases in blood loss and duration of operation. Adhe-

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Address correspondence to Dr. Borland, Department of Anesthesiology, Children's Hospital of Pittsburgh, 125 DeSoto Street, Pittsburgh, PA 15213.

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Table 1. Patient Population

	No.	Age in months mean (range)	Weight (kg) mean (range)	Days from previous liver transplant mean (range)
Obstructive diseases	28	46.9 (12–120)	13.2 (7–19.5)	—
Biliary atresia[a]	22	42.1 (12–96)	13.23 (7–19.5)	—
α-1-antitrypsin deficiency	10	77.4 (30–220)	24.9 (11–66)	—
Failed liver transplant	18	95.6 (18–222)	25.6 (10.8–55)	98.7 (4–700)
Miscellaneous	12	123.9 (7.5–204)	35.1 (6–79.9)	—

[a] Subset of obstructive disease group.

sions are not a problem in patients for repeat liver transplantation occurring within 2–4 weeks of the original operation.

The second stage of the surgical procedure is referred to as the anhepatic phase. After clamping of the suprahepatic inferior vena cava, the infrahepatic inferior vena cava, the portal vein, and the hepatic artery, the diseased liver is removed. Revascularization of the donor liver proceeds first with the anastomosis of the suprahepatic inferior vena cava and infrahepatic inferior vena cava, although the latter anastomosis is not completed at this time. The donor liver is then flushed through the portal vein with 200–300 ml of lactated Ringer's solution. Drainage is from the incomplete infrahepatic inferior vena caval anastomosis. This serves to remove the perfusate, which is rich in potassium, and to clear the liver vasculature of entrained air. The infrahepatic inferior vena cava and portal vein repairs are then completed.

In the third stage, the circulation of the donor liver is reestablished to the recipient. In sequence, clamps on the portal vein, the infrahepatic inferior vena cava, and the suprahepatic inferior vena cava are released. At this time the hepatic artery anastomosis is performed. After adequate hemostasis is achieved, the bile duct is anastomosed. If the patient has a normal extrahepatic ductal system, a duct-to-duct anastomosis with T-tube or indwelling stent is accomplished. If the extrahepatic bile ducts are abnormal, a Roux en Y choledochojejunostomy is performed. Finally, an intraoperative cholangiogram is performed to assess the patency of the biliary drainage system (6,7). Congenital variation in the donor or recipient vessels occasionally requires departure from the technique described above.

Outcome

Thirty-three of our 50 patients are alive two weeks to two years from transplant. The only intraoperative death occurred during an attempted repeat transplant in an 8-yr-old girl who arrived in the operating room with acute liver rejection, chlostridial ascending cholangitis, and septic shock. Manipulation of the necrotic liver acutely elevated serum potassium levels and produced immediate cardiac arrest unresponsive to resuscitative measures. Sixteen additional patients died 2–60 days postoperatively. The causes of postoperative death include acute liver rejection, thrombosis of the vascular anastomosis, and a variety of infectious processes to which immunosuppressed patients are susceptible.

Anesthetic Management

Preoperative Assessment

Thirteen of the 68 patients had hemoglobin values less than 10 gm/dl. The causes of anemia were varied and included nutritional deficiencies, coagulation abnormalities, and upper gastrointestinal bleeding from portal hypertension. As expected, coagulation profiles were frequently abnormal. Prothrombin time (normal values = 10.8 ± 3.0 sec) was abnormal in 35 patients, partial thromboplastin time (normal value = 26–36 sec) was abnormal in 10 and platelet counts were abnormal ($< 100{,}000$ ml^3) in 17.

Previous renal tubular injury, acutely inadequate renal preload, and hepato–renal syndrome contributed to renal dysfunction. Two patients required preoperative peritoneal dialysis. Serum electrolyte disturbances were infrequent, although serum potassium concentrations were occasionally depressed because of chronic diuretic therapy. Hypoglycemia (less than 70 mg/dl) was present in only one patient.

Preoperative hypoxemia was seen frequently. Some patients had a restrictive lung defect (simple lung compression) produced by chronic ascites. More significantly, many patients had an increased alveolar–arterial oxygen difference as a result of diffuse pulmonary arteriovenous shunting. Indeed, cyanosis and clubbing were the presenting signs of liver failure in several patients. Preexisting right to left shunts enhanced the risk of systemic air embolization during the vascular anastomosis (8). Preoperative pulmonary

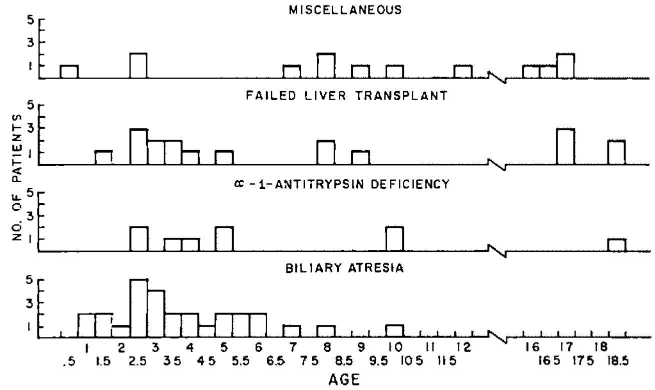

Figure 1. Number of patients vs age in the four patient groups.

function studies failed to demonstrate either peripheral airway obstruction or early onset emphysema in any patient; including those with α-1-antitrypsin deficiency (personal communication, Etsuro K. Motoyama, MD, Director of Pulmonary Function Laboratory/CHP).

Anesthetic and Intraoperative Care

If preoperative coagulation functions were within an acceptable range, patients were premedicated with intramuscular atropine (10–20 μg/kg) or scopolamine (10 μg/kg), morphine sulfate (0.1 mg/kg), and pentobarbital (3–5 mg/kg). If intramuscular injection was contraindicated, atropine (10–30 μg/kg) was given intravenously prior to induction of anesthesia. Before induction of anesthesia, a precordial stethoscope, electrocardiographic leads, and a blood pressure cuff were put in place.

After induction, additional monitoring included placement of rectal and esophageal temperature probes, an esophageal stethoscope, and an indwelling urinary catheter. Inspiratory and expiratory gases were monitored with a Perkin-Elmer mass spectrometer. End-tidal carbon dioxide and nitrogen were monitored to assist in recognizing the occurrence of air embolization. Four intravenous cannulae (all in the upper extremities) were then inserted, as well as an arterial cannula (usually placed percutaneously in the radial artery) and a central venous pressure catheter (via the external or internal jugular route, but occasionally via the antecubital vein in older children). A flow-directed, balloon-tipped pulmonary arterial catheter (Swan–Ganz) was placed in 28 patients. All pressures were displayed on a four-channel Hewlett-Packard monitor. Ample padding of extremities and all pressure points (including the head) concluded preparations prior to the incision.

Table 2. Etiology of Liver Failure—Miscellaneous Diseases

Disease	No.
Wilson's disease	3
Chronic active hepatitis	2
End stage liver disease etiology?	1
Neonatal hepatitis	1
Tyrosinemia	1
Glycogen storage disease type I	1
Biliary cirrhosis	1
Sea blue histiocyte syndrome	1
Hepatic tumor	1

Intravenous access had been established in most patients either for pretransplant infusion of cyclosporin-A (9,10) or for ICU management. Intravenous induction of anesthesia (in 54 patients) was accomplished with thiopental (3–5 mg/kg). Occasionally, ketamine (1–2 mg/kg), fentanyl, or morphine was used for both induction and maintenance. Inhalation induction was performed in 12 cases. Four patients arrived in the operating room with an endotracheal tube in place. Intramuscular ketamine (5–7 mg/kg) was given as the induction agent in two patients.

If the patient had a full stomach, preoxygenation preceded intubation utilizing the Sellick maneuver after intravenous thiopental (3–5 mg/kg) or occasionally ketamine (1–2 mg/kg) and succinylcholine (1 mg/kg). Oral tracheal intubation was performed in 50 patients and nasal intubation in 18. Because the duration of surgery and the cardiovascular status of these patients varied greatly, a number of anesthetic agents was used for maintenance of anesthesia. Halothane was used for both induction and maintenance in nine cases but in only one patient after revascularization of the donor liver. Isoflurane was utilized in the remaining 37 cases in which an inhalation agent was used and was frequently added to a balanced anesthetic technique for control of systemic arterial hypertension. Nitrous oxide–narcotic–muscle relaxant was used in 59 cases, fentanyl in 44, morphine in 13, and meperidine in 2. Pancuronium was the nondepolarizing neuromuscular relaxant of choice in 62 cases; metocurine was used in 6.

Intraoperative laboratory measurements fell into two categories: "stat" (immediate) and "as soon as possible." Arterial blood gas tensions and pH, hemoglobin, hematocrit, colloid osmotic pressure and serum levels of sodium, potassium, and ionized calcium were measured in the anesthesia–intensive care laboratory within 10 min. Serum levels of chloride, total calcium, creatinine, glucose, complete blood count, prothrombin, and partial thromboplastin times were obtainable within 1 hr from the central laboratories. When the clinical situation required immediate estimation of serum glucose, Dextrostix analysis of whole blood was used in the operating room suite.

Observations and Discussion

Unlike the vast majority of pediatric surgical patients, children receiving orthotopic liver transplants characteristically suffer from multisystem disorders that provide a number of medical challenges. Equally important, however, is the necessity for handling logistical problems by advance planning. Coördination of patient transport, operating room, and surgical and anesthetic teams is essential. Establishment of a clear and consistent chain of communication and responsibility must precede the actual surgery. Timing of the surgical incision must await notification of donor liver acceptability, because donor organ viability from the time of harvesting to the time of revascularization is 8 hr. The duration of this type of surgery frequently disrupts the operating room schedule for elective cases. The ability to provide anesthetic and operating room personnel for liver transplantation without compromising the delivery of care for other urgent surgery patients must be assured before initiation of a liver transplant program. Simultaneous donor and recipient surgery clearly strained our capability to provide additional emergency care.

The requirements for additional personnel do not stop with the operating room; the increased demands on laboratory and blood bank personnel must also be anticipated. A runner responsible solely for the transport of specimens and blood products is indispensable. The impact of long-term use of regular and critical care hospital beds must be considered. The immediate postoperative stay in the intensive care unit varied from 2 days to more than 30 days (mean, 6.5 days). The average hospital stay was 59 days. Lastly, the effect of fatigue (average procedure time, 655 min; maximum time, 1170 min) on the medical and paramedical personnel and, therefore, on patient care must also be borne in mind.

Early in this series, nitrous oxide–fentanyl–pancuronium was the most frequently chosen anesthetic technique. Hemodilution secondary to massive bleeding and transfusion increased the required dose of intravenous narcotic agents. Nitrous oxide was usually discontinued during the antihepatic phase of surgery because of bowel distension and the risk of air embolization. Fortunately, patient awareness as a result of discontinuing nitrous oxide and the washout of intravenous anesthetic agents was an unrealized concern. More recently, isoflurane anesthesia (with or without nitrous oxide) has been used.

Despite possible disturbances in pseudocholinesterase production (11), prolongation of the action of succinylcholine was not a clinical problem because of the duration of surgery and the dilutional effect of multiple blood volume exchanges. Because hepatic and renal routes of pancuronium elimination were also frequently impaired, clinically significant prolongation of neuromuscular blockade was observed (i.e., the time between maintenance doses was prolonged). This abnormality lessened after revascularization of the donor liver. Neuromuscular monitoring, including train-of-four measurement, for accurate titration of nondepolarizing agents was extremely useful. Virtually all patients were making spontaneous respiratory efforts on arrival in the pediatric intensive care unit.

The extent of hypoxemia secondary to parenchymal disease or pulmonary arteriovenous shunting should be assessed preoperatively. Multiple infradiaphragmatic vascular anastomoses and preexisting pulmonary arteriovenous shunting make systemic air (or particulate) emboli a serious possibility (8,12). When tolerated by the patient, PEEP 5-cm H_2O was utilized to increase intrathoracic pressure to minimize the possibility of air embolus. In an attempt to limit barotrauma and to produce a quiet surgical field, high-frequency jet ventilation (HFJV) was used in three patients. One patient experienced profound massive systemic air embolization during HFJV. The contribution of HFJV to this intraoperative catastrophe was not determined. Although this patient recovered almost completely from the neurologic injury sustained, use of HFJV has been terminated. In spite of abdominal compression and fluid imbalance (which led to massive pulmonary edema on two occasions), Pa_{O_2} and Pa_{CO_2} were maintained in the normal range utilizing conventional ventilation with an inspired oxygen concentration less than 50%. Hypercarbia unresponsive to conventional ventilation occurred only once.

Preservation of intravascular volume and myocardial stability was one of the greatest challenges in these patients. Systemic arteriovenous shunting improved intravenous access. All catheters were placed in the upper extremities or neck. While all initial intravenous solutions were crystalloid, correction of abnormal coagulation (13,14) (determined by hourly measurement of prothrombin and partial thromboplastin times) often required fresh frozen plasma, 1 ml for each ml of packed red blood cells. Preexisting or dilutional thrombocytopenia mandated hourly measurements of platelet counts; transfusion of platelets was almost always necessary (15–17). Only one of the four intravenous infusions consisted of glucose

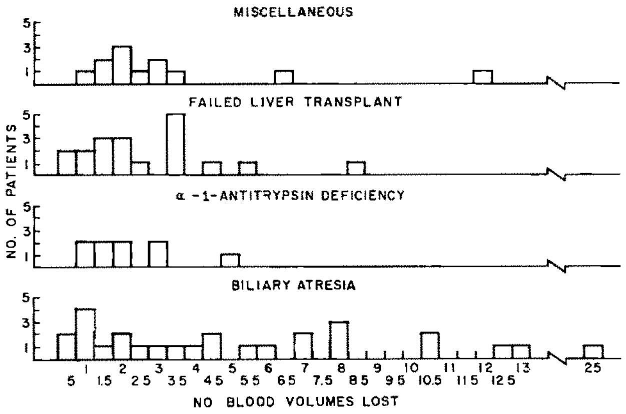

Figure 2. Number of patients vs number of blood volumes lost (4 patient groups).

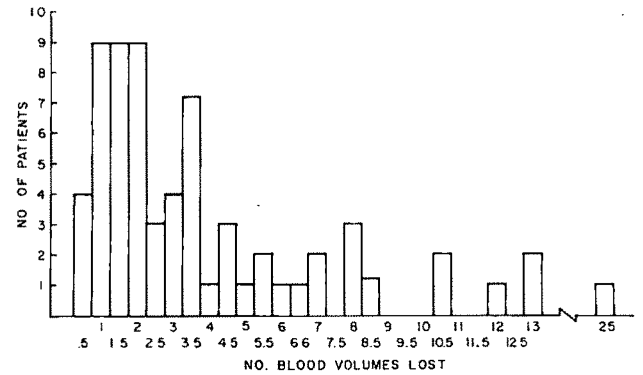

Figure 3. Number of patients vs number of blood volumes lost (n = 68, all patients).

as 5% dextrose in lactated Ringer's solution or 0.2% normal saline. Careful titration of infused crystalloid and colloid (fresh frozen plasma) solutions, facilitated by measurements of colloid osmotic pressure, central venous pressure (CVP), or pulmonary artery wedge pressure (PAWP), helped decrease the incidence of intraoperative pulmonary edema. A cell saver device should be used only if salvaged units of blood are spun to a hematocrit of 70–80%. Unfortunately, we found that the salvaged blood was frequently contaminated with non-blood products and, therefore, could not be reinfused. Veno–venous bypass was used during surgery in 4 patients in an attempt to minimize blood loss; the perfusion device also served as a rapid infusion pump. Difficulty in reversing heparinization forced the elimination of this approach. New heparin-bonded perfusion systems have not been tried.

Blood loss was highest in patients with biliary atresia (mean, 5.4 blood volumes (range 0.6–25) Fig. 2). Adhesions from previous surgery increased both the operating time and the blood loss during the first stage of surgery. Blood loss during this period was not predictive of subsequent loss. The mean blood loss for all 68 cases was 3.95 blood volumes (range 0.5–25) (Fig. 3). Blood loss is given in blood volumes instead of ml replaced to allow comparison among patients with a wide range of body sizes. Estimated blood loss ranged from 370 to 30,000 ml.

In contrast to early reports from the University of Colorado (18) intraoperative hypoglycemia has been infrequent. Only two patients had serum glucose levels less than 90 mg/dl but both were more than 65 mg/dl. Transfusion of packed red cells (containing 0.5 gm glucose/unit) invariably increased serum glucose levels, even when we limited or eliminated glucose-containing crystalloid products. Just before removal of the diseased liver, the mean serum glucose level was 274 ± 129 mg/dl and increased to 383 ± 165 mg/dl 1 hr after revascularization of the donor liver (Fig. 4). This hyperglycemia was refractory to treatment by bolus injection of regular insulin (0.1 unit/kg) during the anhepatic phase. Although hyperosmolarity has been reported to cause central nervous system injury (19), elevated serum glucose levels did not produce undesired sequelae in this series. Because the liver is the major site of action of insulin, this refractoriness is not surprising. After revascularization of the liver was complete, serum glucose levels decreased spontaneously as the new liver began to metabolize glucose. Insulin appeared effective at this time although it was used infrequently.

Elevated serum glucose levels sometimes produce an osmotic diuresis. This increased urine output must not be mistaken as an indication of adequate intravascular volume. Despite adequate intravascular volume (renal preload), administration of furosemide or dopamine (5 μg/kg/min), and the elevated serum glucose levels, oliguria and anuria occurred nevertheless in 28 cases. During the first stage of surgery, hepatorenal syndrome was assumed to be the cause of decreased urine output (20). Virtually all patients were anuric or profoundly oliguric during the anhepatic phase. When the inferior vena cava was cross-clamped, the arterio–venous pressure gradient across the kidney decreased. This clearly affected renal blood flow. After revascularization of the liver and decompression of the vena cava, urine output usually increased markedly. This may have been a result of the return of normal renal blood flow or the resolution of the hepatorenal syndrome.

Hypotension occurred because of several factors: inadequate fluid replacement in response to massive and rapid blood loss; cardiac dysfunction secondary to decreased concentration of ionized calcium (presumably as result of increased citrate concentration

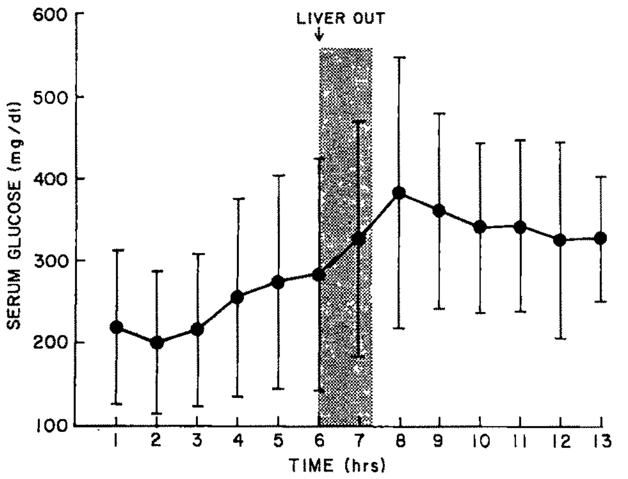

Figure 4. Serum glucose vs time, $n = 42$, mean and SD are represented. The shaded area represents the anhepatic period.

after massive transfusion with packed red cells); preexisting myocardial disease; surgical manipulations that disturbed preload, e.g., occlusion of the inferior vena cava during the anhepatic phase; and life-threatening arrhythmias.

Unique cardiovascular changes occur during the vascular clamping and reanastomosis. The clamping of the infrahepatic inferior vena cava at the onset of the anhepatic stage produces a precipitous decrease in preload to the heart (21). Collateral circulation secondary to portal hypertension modulates this decrease in preload from the infradiaphragmatic portion of the body. During revascularization of the liver, the infrahepatic inferior vena cava is opened first. The intravascular bed enlarges to include the donor liver (22), but volume preloading prevents a resultant decrease in systolic arterial pressure. Next, the suprahepatic inferior vena cava is opened. A transient (5–10 min) decrease (30–50 torr) in the systolic and diastolic arterial pressures often occurs at this time, despite volume preloading. Venous stasis in the lower extremities and the bowel occurs as a result of inferior vena caval occlusion. Myocardial contractility, furthermore, may have decreased as a result of the bolus infusion of acidotic blood. The mean pH decrease was 0.15. A transient increase in serum potassium may have produced systemic vasodilation. In our series, the mean increase in potassium was 1 mEq/L. Nevertheless, hypotension was observed even when pH and serum potassium remained stable. We are currently investigating the contribution of kallikrein-like substances to this hypotension. Crystalloid or colloid infusion, a bolus of calcium chloride (15 mg/kg), and brief administration of dopamine (10–15 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) were required to return systemic blood pressure toward values measured before the cross-clamp release.

The range of serum potassium levels during the intraoperative period was wide (1.5–11.0 mEq/L). Acute hyperkalemia at the release of the vascular cross clamp was a major problem. Cardiac arrest secondary to "potassium cardioplegia" from the donor liver occurred in three patients. Cardiac compression and pharmacologic therapy (i.e., sodium bicarbonate, calcium chloride, glucose, and regular insulin) were effective in lowering serum potassium levels and in restoring normal rhythm and systolic arterial blood pressure. At the time of surgical removal from the donor, the liver is infused with cold lactated Ringer's solution; it is not perfused during transport. Significant extracellular shift of potassium occurs. Washout of the liver infusate before completion of the infrahepatic inferior vena cava anastomosis is, therefore, mandatory. During the revascularization period, uptake of potassium by the donor liver and intracellular shift of potassium secondary to metabolic alkalosis contributed to hypokalemia. Supplemental potassium therapy may be required at this time (23–25).

Sodium imbalance has been described as a common occurrence during liver transplantation (18). In six cases in our series, hyponatremia ($Na^+ < 130$ mEq/L) was noted during part of the surgical procedure; hyponatremia had been present preoperatively in all six cases. One patient remained hyponatremic during the entire procedure. Hypernatremia ($Na^+ > 150$ mEq/L) occurred in three patients. Administration of sodium bicarbonate during cardiopulmonary resuscitation contributed to the hypernatremia in one instance. The etiology of the hypernatremia was not determined in the other two patients.

Preoperative acid–base balance as reflected by base excess varied widely among patients. Figure 5 describes the change in base excess over the operative course. All patients exhibited increasing metabolic acidosis until the beginning of revascularization (23). In an attempt to avoid late onset metabolic alkalosis, the administration of sodium bicarbonate was minimized in all cases; 34 patients received no sodium bicarbonate intraoperatively. Nevertheless, severe postoperative metabolic alkalosis developed because of the metabolism of exogenous citrate to bicarbonate and the loss of chloride from the use of furosemide. Lactate in crystalloid solutions is metabolized to bicarbonate and may also contribute to the development of metabolic alkalosis. Moderate metabolic alkalosis (base excess +5 to +10) was present in all patients undergoing repeat liver transplantation within 2–4 weeks of the initial procedure. Normal saline (0.9%)

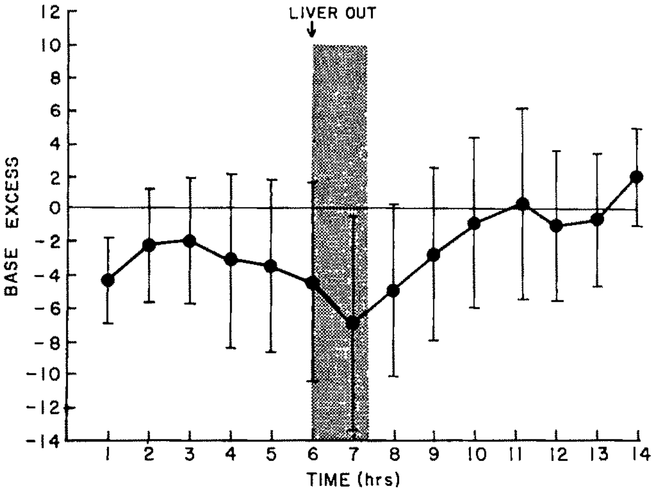

Figure 5. Base excess vs time, $n = 42$, mean and SD are represented. The shaded area represents the anhepatic period.

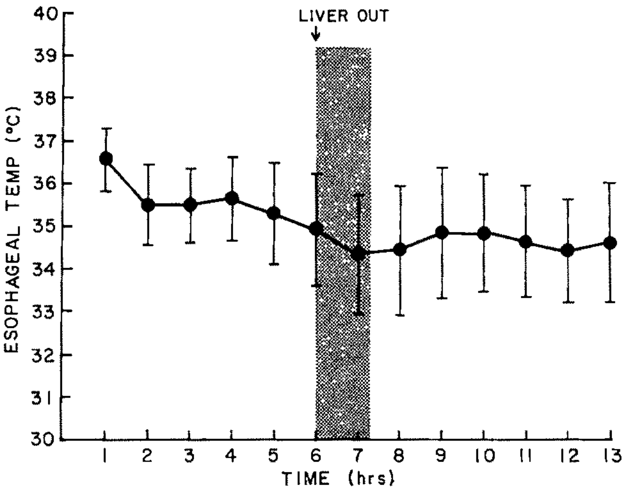

Figure 6. Esophageal temperature vs time, $n = 36$, mean and SD are represented. The shaded area represents the anhepatic period.

may be a more appropriate solution for this procedure.

Unintentional hypothermia (esophageal temperature < 35.5°C) was a problem in 58 cases. This has been reported previously (26). A warming blanket, heated humidifier, and a head wrap were used in an effort to conserve body heat. All blood products and crystalloid solutions were warmed. Requests that the surgeons wrap the bowel with warm surgical sponges, use a laparotomy bag, and warm irrigating solutions frequently went unheeded. Figure 6 demonstrates the trend in esophageal temperature.

Reports of citrate intoxication secondary to massive blood transfusion note that the resulting myocardial dysfunction is transient unless hypothermia or hepatic disease is present (27–30). Both occurred in all of our cases. Measurement of ionized calcium is imperative for optimal management of the cardiovascular function during liver transplantation. Rapid determination of ionized calcium levels was available in 21 cases (late in the series). During or immediately after periods of rapid blood transfusion and in spite of adequate preload (determined CVP, PAWP, or both), systemic hypotension often occurred. A 500-ml unit of whole blood contains 1.656 g hydrated trisodium citrate prior to further processing; the amount of citrate in a unit of packed red cells is variable. The volume and rate of transfusion correlated with decreased levels of ionized calcium. Total calcium levels did not correlate with serum ionized calcium. Forty-six patients were given supplemental calcium chloride (15 mg/kg in repeated doses); several patients received continuous calcium chloride infusion intravenously. Calcium gluconate is not recommended, because the liver is required for its metabolism.

Because of the possibility of preexisting myocardial disease, profound metabolic derangements (especially decreased ionized calcium) that might affect cardiac output, and the requirement for massive fluid infusion, the insertion of a pulmonary arterial catheter would seem to be desirable. We used pulmonary arterial catheters in the 28 cases in which they could be placed successfully. However, CVP and PAWP measurements rarely revealed right–left heart dissociation, nor were PAWP measurements necessary for clinical management during the immediate postoperative period (postoperative days 1–3). During the vascular anastomosis, surgical compression of the diaphragm and heart produced marked variation in both CVP and PAWP measurements. Monitoring of the intravascular volume status with either CVP or PAWP during this period was clinically unsatisfactory. Measurement of cardiac output and calculated systemic vascular resistance may prove useful in the rational management of hypotension that occurs after revascularization.

Abdominal closure was impossible in one patient because of gut distention and the large size of the donor liver. During attempts at closure, ventilation was grossly inadequate despite airway pressures exceeding 50 cm H_2O. Temporary closure was ultimately accomplished with a silastic silo similar to that used in the repair of a large omphalocele. Infrequent problems included one case each of phrenic nerve injury, recurrent laryngeal nerve injury, massive systemic air embolization, and pneumothorax; massive subcutaneous blood infusion occurred in two cases.

In summary, the intraoperative problems encountered during 68 pediatric liver transplant operations were metabolic (biochemical) and hemodynamic in nature. Intraoperative hypoglycemia was not a problem in this series. Cardiovascular changes were difficult to manage before and after the anhepatic phase, and hyperkalemic cardiac arrest at the time of revascularization remains a major risk. Unintentional hypothermia and decreased ionized calcium levels contributed to the instability of cardiac rhythm and contractility. Whereas there was a difference in the number of blood volumes lost with each diagnostic category of patients, individual patient variation was great. Massive blood loss was the rule in all cases. In spite of significant preoperative coagulation factor deficits, the intraoperative anhepatic period, and massive blood losses, hemostasis was achieved with infusion of fresh frozen plasma and platelets as indicated by prothrombin and partial thromboplastin measurements and platelet counts.

The members of the Department of Anesthesiology of the Children's Hospital of Pittsburgh labored many long hours in the care of these patients. This review exists because of their dedication and skill.

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ANESTH ANALG
1985;64:125–8

Hemodynamic Responses in Brain Dead Organ Donor Patients

Randall C. Wetzel, MD, Nancy Setzer, MD, Judith L. Stiff, MD, and Mark C. Rogers, MD

WETZEL RC, SETZER N, STIFF JL, ROGERS MC. Hemodynamic responses in brain dead organ donor patients. Anesth Analg 1985;64:125–8.

Because we have noticed dramatic hemodynamic responses in brain dead patients undergoing surgery for organ donation, we analyzed the anesthetic records of cadaver organ donors. Ten records contain complete data for heart rate, blood pressure, central venous pressure, and time of incision. Systolic pressure increased by a mean of 31 torr ($P <$ 0.01), diastolic pressure by 16 torr ($P < 0.02$), and heart rate by 23 beats/min ($P < 0.01$) in response to surgical stimulation. These results demonstrate the occurrence of significant hemodynamic responses to surgical stimuli in patients who fulfill the criteria of brain death, responses that do not, however, invalidate the current criteria for the diagnosis of brain death.

Key Words: SURGERY—transplantation. BRAIN—organ donor functions.

There still remains an uneasiness about the provision of meticulous care to a human being who may be physiologically stable but legally dead, and this is enhanced by the fact that sophisticated medical care is suddenly and irrevocably withdrawn once organs are harvested from such patients. Furthermore, the declaration of brain death is commonly thought to imply that the patient has become totally unresponsive to all stimuli. It has been our experience that certain hemodynamic responses occur in cadaver donors that superficially mimic the responses of live patients and can cause concern as to whether or not these patients are indeed suitable organ donors. There may also remain a need for cautious hemodynamic management to preserve the function of the donated organs. This report highlights these points by documenting significant hemodynamic responses to painful stimuli in cadaver organ donors.

Case Report

A 33-yr-old man suffered a massive subarachnoid hemorrhage 36 hr prior to operation for donation of heart and kidneys. He had no significant past medical history, no previous operations, and no medical illnesses. On admission to the hospital, he was unresponsive, with fixed, dilated pupils and absent cranial nerve reflexes. Mechanical ventilation was instituted with fluid restriction. The patient subsequently developed diabetes insipidus, which required large volume infusion and continuous intravenous vasopressin. Despite vigorous therapy, the patient was declared brain dead by the criteria defined by the Medical Board of The Johns Hopkins Hospital. These criteria are compatible with those reported from other centers (1–5). His family consented to organ donation and the decision was made to use the patient's heart and kidneys for transplantation to nonrelated living recipients.

The patient was brought to the operating room while receiving vasopressin and volume replacement for urine loss resulting from diabetes insipidus. He was being mechanically ventilated with 100% oxygen. At the time of admission to the operating room, the blood pressure was 90/50 torr, with a pulse of 90 beats/min and a central venous pressure (CVP) of 8 torr. Hematocrit was 38% and the serum electrolyte levels were normal. Fluid replacement and vasopressin were discontinued 10 min before incision. The patient was receiving no pressor agents. Immediately prior to abdominal incision, the blood pressure was 90/50 torr, the CVP was 8 torr, and the heart rate was 90 beats/min. As can be seen in Figure 1, within seconds of incision, the blood pressure increased to 120/70 torr, while the CVP remained unchanged, and the pulse increased to 104 beats/min. Within 3 min after incision, the blood pressure had increased to 150/75 torr and the pulse to 112 beats/min; the CVP remained unchanged. Over the next several minutes, the pulse continued to increase to 118 beats/min, the CVP decreased to 5 torr, and the blood pressure eventually reached a peak of 180/90 torr. During this time, there

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Received from the Department of Anesthesiology/Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland. Accepted for publication October 18, 1984.

Address correspondence to Dr. Wetzel, Department of Anesthesiology/Critical Care Medicine, The Johns Hopkins Hospital, 600 N. Wolfe Street, CMSC 7-110, Baltimore, MD 21205.

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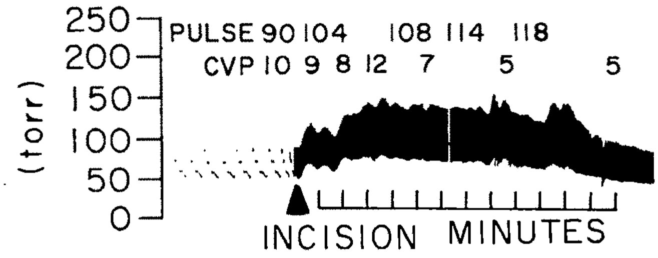

Figure 1. Arterial pressure response to abdominal incision in case reported in text. Arterial pressure is on the ordinate and time on the abscissa. Heart rate per minute and central venous pressure (CVP, torr) is shown at the top. Increases in heart rate and a decrease in CVP accompanied the increase in blood pressure that started immediately after incision. At 11 min, 2% enflurane was begun as an anesthetic agent.

Table 1. Pulse and Blood Pressure Changes in the 10 Organ Donors

	Blood pressure		
	Systolic (torr)	Diastolic (torr)	Heart rate (beats/min)
Before incision	100	58	104
(±SD)	(24)	(18)	(28)
Maximal	131	74	127
(±SD)	(23)	(16)	(24)
Change			
Mean	31	16	23
Range	10–70	0–40	0–50
P value	0.002	0.019	0.002

were no pupillary responses, no respiratory effort, no movement, and no diaphoresis. No anesthetic agents were administered before this pressor response. No ECG changes were noticed and end-tidal CO_2 was constant at 35 torr.

Chart Review

The records of additional patients who were cadaver organ donors over the past 36 months were reviewed to determine whether heart rate and blood pressure responses to surgical stimuli occurred in these donors. Nine records were obtained with complete data for incision times, drug and fluid administration, pulse, and systolic and diastolic blood pressure responses in response to surgical stimulation. All patients selected as cadaver donors had met the hospital's criteria for brain death. In two of these patients (aged 2 and 3 yr), brainstem auditory and somatosensory evoked responses were recorded before the declaration of brain death as part of their neurological evaluation. Intraoperative care was designed to assure that organ perfusion was maintained. All patients were maintained on 100% inspired oxygen. Four patients received phenoxybenzamine before incision as part of the kidney harvesting protocol. Systolic and diastolic blood pressures and pulse rates were recorded before incision and during surgery, and the maximal responses and the time at which they occurred were noted. The data obtained from the chart review and the case report were analyzed together by paired Student's *t*-test.

Results

All patients ($N = 10$) showed dramatic increases in systolic and diastolic blood pressures as well as in heart rate after incision (Table 1). Elevations above baseline occurred within the first minute after incision and maximum responses were seen between 5 and 20 min. These peak changes in pressure and heart rate were reached before aortic cross clamping or the occurrence of any other surgical procedure that could be expected to mechanically elevate blood pressure or cause an increased heart rate. In those patients who required pressor administration to maintain blood pressure before surgery, the increase in pressure was not related to a change in rate or type of drug administered. In fact, in all cases it was possible to decrease or discontinue pressor support in response to the elevated blood pressure produced by surgical stimulation. The average intravascular fluid administration after arrival in the operating room was 350 ± 270 (SD) ml/hr and urine output was 205 ± 175 (SD) ml/hr. Changes in pulse and blood pressure were not temporally related to fluid administration. All of the donors' blood pressures returned to baseline within 25 min of incision.

In two patients the brainstem auditory evoked response to click stimuli showed only one wave unilaterally in one patient, although all other records were isoelectric. This wave represents peripheral auditory nerve activity. After median nerve stimulation in these two patients, cortical evoked responses were totally absent, but in both patients a single wave with a mean latency of 9 msec was recorded by an electrode over the second cervical vertebrae (C2). This wave is thought to represent upper spinal cord or lower medullary electrical activity (6,7).

Discussion

This case report and review of the operative records from nine cadaver organ donors demonstrate that significant hemodynamic responses to operative stimuli occur in patients who have fulfilled the commonly accepted criteria for the diagnoses of brain death. While this observation may, on reflection, not be surprising, the circumstances under which these responses are noted may not allow for reflection. These hemodynamic changes many frequently produce uneasiness in the medical and nursing staff. There are, however, physiologic reasons that may explain these responses.

In normal patients, pressor responses to painful stimuli are mediated through ascending afferent fast and slow pain fibers that pass via the anterolateral spinothalamic tracts to the thalamic nuclei and thence through radiations to the somatosensory cortex (8,9). Relays to the hypothalamus, where sympathetic function is integrated, arise at several levels including the thalamus and cortex (10). Descending pathways include the vasomotor center in the medulla that, via the sympathetic nervous system, sends efferents to the thoracolumbar sympathetic ganglia. Peripheral afferents to the vasomotor center also arise from the baroreceptors and chemoreceptors; these, too, require an intact brainstem to give rise to integrated responses (8,10).

Although the pressor response to nociceptive stimuli is well known and involves brainstem function, there may be other explanations for a pressor response to surgical stimuli that do not involve brainstem function. A clear example is seen in patients who have a high total transection of the spinal cord. These quadriplegic patients have a "mass reflex," including systemic hypertension, in response to a variety of noxious stimuli (11,12). The existence of peripheral or spinal vasoconstrictor responses may explain the occurrence of a sympathetic reflex to noxious stimuli in this setting and may involve intact spinal reflex arcs between pain and sympathetically mediated efferents (12). Other potential mechanisms of a hypertensive response to noxious stimuli may include humoral responses such as adrenal medullary stimulation by reflex spinal arc (10,13). The occurrence of the pressor response to pain within days after injuries is not, however, characteristic of the mass reflex.

There are, of course, other potential pharmacologic and physiologic explanations that may partially explain the increased blood pressures seen in the brain dead patients reported here. For example, increased intravascular volume could explain an increased blood pressure; however, in the patient studied prospectively with continual recordings of arterial and central venous pressures, it is quite clear that the response immediately followed incision (Fig. 1) and is not accompanied by an increased central venous pressure. Furthermore, fluid administration was either discontinued or not altered in the patients reported here. In addition, the occurrence of a pressor response with an increased heart rate leads us to believe that this response, which occurred in all patients, was not due to increased intravascular volume.

Identifying responses in brain dead patients that are not routinely assessed, but which potentially may indicate partial brainstem function, as in this report, presents a perplexing problem. The rigid criteria for the declaration of brain death have traditionally been taken to imply total cessation of all central neuronal function (1–4). However, it has been asserted that brainstem death is the crucial element in the diagnosis of brain death (5,14,15). It is, however, not the purpose of the current criteria for the diagnosis of brainstem death to identify total cessation of function of all brainstem neurons, but rather to define the degree of loss of function at which irreversible brainstem damage has occurred, and from which brain death is inevitable (1–5,14,15). Mohendas and Chou (14) stated, "What we are attempting to define and establish beyond reasonable doubt is the state of irreversible damage to the brainstem. It is the point of no return." This concept of brainstem death has been further expanded upon (1–5,14,15). The current criteria for the diagnosis of brain death include absent bulbar reflexes and no apparent central regulation of respiratory function; all conceivable brainstem and medullary reflexes are not considered in the determination of brain death. The recognition of partial brainstem function, other than that currently identified by the clinical brain death criteria, may be expected as increasingly sophisticated technology is used to examine brainstem function.

In two of our patients, cortical evoked responses were obtained. The short latency somatosensory responses demonstrated a single wave with a mean latency of 9 msec recorded over C2 in both patients. This response has been considered consistent with the diagnosis of brain death (6,7). Although the origin of this electrophysiologic finding is not clear, it may potentially arise near the cervicomedullary junction and, therefore, may indicate some residual lower medullary function (16,17). The presence of this wave may indicate at least partial brainstem function in our two patients who were clinically brain dead and who showed a pressor response to surgical stimuli.

Whatever the underlying mechanism of the hemodynamic responses in patients who have been declared brain dead, their occurrence appears to be common during donor organ harvesting and can be expected to occur in response to other noxious stimuli. Although these responses may suggest partial lower medullary function, the medical personnel caring for the donor should be reassured that such a response does not invalidate the diagnosis of brain death.

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Midazolam–Ethanol Interactions and Reversal with a Benzodiazepine Antagonist

Paul N. Van Gorder, MD, William E. Hoffman, PhD, Verna Baughman, MD, Ronald F. Albrecht, MD, David J. Miletich, PhD, Filadelfo Guzman, PhD, and James M. Cook, PhD

VAN GORDER PN, HOFFMAN WE, BAUGHMAN V, ALBRECHT RF, MILETICH DJ, GUZMAN F, COOK JM. Midazolam–ethanol interactions and reversal with a benzodiazepine antagonist. Anesth Analg 1985;64:129–35.

The purpose of these experiments was to analyze the cerebrovascular and cerebral metabolic effects of midazolam, a short-acting water-soluble benzodiazepine, and to investigate its interaction with alcohol in rats. A benzodiazepine antagonist, 3-carbo-t-butoxy-β-carboline (β-CCT), was used to test the role of the benzodiazepine receptor in midazolam–alcohol effects. Experiments were carried out under 70% N_2O, 30% O_2 anesthesia. Rats were tested with intraperitoneal injections of 0.75–5 mg/g ethanol, intravenous infusions of 0.57, 5.75 mg/kg midazolam, and 1.15 mg/kg β-CCT separately and in combination. Cortical cerebral blood flow (CBF) was measured with radioactive microspheres, and cerebral oxygen consumption ($CMRo_2$) was determined from cortical CBF and arterial–sagittal sinus blood samples 20 min after ethanol treatment and/or after a 15-min drug infusion. Alcohol alone produced dose-related increases in plasma ethanol concentrations but no depression in $CMRo_2$ except at the highest dose (5 mg/g). Midazolam infusions alone decreased cortical CBF and $CMRo_2$ 35–40%, while 2.5 mg/g alcohol (which did not depress $CMRo_2$ alone) combined with midazolam produced a 70% depression of cortical CBF and metabolism. An infusion of β-CCT given alone increased $CMRo_2$ alone and reversed the depression in both cortical CBF and $CMRo_2$ produced by midazolam plus alcohol. These results indicate that the ability of alcohol to potentiate benzodiazepine-induced sedation is not simply an additive effect but may be related to the facilitation by alcohol of benzodiazepine receptor binding. The fact that β-CCT reversed midazolam–ethanol-induced depression suggests that the effect may be mediated through the benzodiazepine receptor.

Key Words: HYPNOTICS—BENZODIAZEPINES, midazolam. BRAIN—BLOOD FLOW, metabolism. ALCOHOL. INTERACTIONS (DRUG)—midazolam, alcohol.

In clinical use, benzodiazepines produce sedation and muscle relaxation, and have anxiolytic and anticonvulsant properties. Their interaction with alcohol that produces enhanced cerebral depression is well known, but has not been characterized physiologically or on a molecular level. High-affinity stereospecific benzodiazepine receptors have been identified in brain tissue that mediate the pharmacologic effects of benzodiazepines (1,2). Burch and Ticku (3) indicate that ethanol enhances benzodiazepine binding. An increase in (H^3)–diazepam binding was observed with ethanol concentrations ranging from 10 to 100 mM. If ethanol potentiates the cerebral depression produced by benzodiazepines and this potentiation is mediated by the benzodiazepine receptor, then a specific benzodiazepine antagonist should reverse both benzodiazepine- and benzodiazepine-plus-ethanol-induced cerebral depression. The purpose of this experiment was to investigate the cerebrovascular and cerebral metabolic effects of the short-acting water-soluble benzodiazepine, midazolam; the interaction of ethanol with midazolam; and the ability of a benzodiazepine antagonist, 3-carbo-*t*-butoxy-β-carboline (β-CCT), to reverse midazolam and midazolam–alcohol effects.

Methods

Surgical Preparation

Six-month-old male Sprague–Dawley rats were anesthetized with halothane in a bell jar, tracheotomized, and ventilated with 1% inspired halothane in

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Address correspondence to Dr. Hoffman, Anesthesiology Department, Michael Reese Hospital and Medical Center, Chicago, IL 60616.

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O_2 using a Harvard small-animal respirator. Body temperature was maintained at 37°C and arterial blood PCO_2 was maintained between 35–40 mm Hg by adjusting ventilation. Bilateral cutdowns were performed for cannulation of both femoral arteries and both femoral veins with Clay–Adams Intramedic polyethylene catheters filled with heparinized normal saline solution. These catheters were used for continuous heart rate and pressure monitoring, blood withdrawal, and drug administration. The left ventricle was catheterized via the right common carotid artery for microsphere injections. Pressure tracings were monitored to ensure proper catheter placement. A Hewlett–Packard pressure transducer and chart recorder was used in all cases. The skull was exposed, a small hole drilled into the sagittal sinus, and a catheter inserted for withdrawal of sagittal sinus blood samples. After completion of surgery, halothane was discontinued and the animal was maintained on 50% N_2O and 50% O_2 for a 45-min equilibration period. Muscle relaxation was achieved with 1 mg/kg of intravenous *d*-tubocurarine.

Drug Administration

Animals were assigned to one of several treatment schedules. In part one, rats were selected to determine the effects of intraperitoneally injected alcohol in various doses on cerebral blood flow and metabolism. Doses were 0.75, 1.25, 2.5, and 5.0 mg absolute ethanol per gram body weight. Microsphere injections and blood-gas measurements were made 20 min after the injection of alcohol.

In part two, rats were subjected to one of the following treatments: 1) an intravenous bolus injection of 0.2 or 2 mg/kg midazolam followed by a 15-min infusion of 0.025 or 0.25 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ for a total dose of 0.575 or 5.75 mg/kg midazolam, respectively; 2) an intraperitoneal injection of 2.5 mg/g ethanol followed 5 min later by a 15-min intravenous infusion of midazolam for a total dose of 0.575 mg/kg; 3) an intravenous bolus injection of 0.4 mg/kg β-CCT followed by a 15-min infusion of 0.05 mg/kg for a total dose of 1.15 mg/kg; 4) simultaneous 15-min intravenous infusions of 0.575 or 5.75 mg/kg midazolam combined with 1.15 mg/kg β-CCT (total doses); or 5) an intraperitoneal injection of 2.5 mg/kg ethanol followed by a 15-min combined infusion of 0.575 mg/kg of midazolam and 1.15 mg/kg of β-CCT test procedures. Microsphere injections were made 20 min after alcohol and after the 15-min drug infusions. The drug infusions were maintained throughout the microsphere test procedure.

Microspheres

Microsphere injections were performed according to previously described techniques (4) using 15-μ microspheres labeled with cobalt-57, ruthenium-103, or scandium-146 (New England Nuclear). Stock solutions containing 500,000 microspheres/ml were suspended in isotonic saline with 0.1% Tween-80. Ventricular pressure tracings were monitored before each microsphere injection. Microspheres were vortexed for 1 min, withdrawn (0.2 ml—100,000 microspheres), injected into the left ventricle via the ventricular catheter (dead space = 0.06 ml), and flushed in with 0.2 ml of saline. Starting immediately before each microsphere test and continuing 45 sec after the end of each injection, blood was withdrawn from a femoral artery at a rate of 0.4 ml/min using a Harvard infusion-withdrawal pump. Arterial blood–gas measurements were made at the end of each microsphere injection procedure. Arterial and sagittal sinus blood samples were also taken after each microsphere test for measurement of cerebral arterial–venous O_2 content (AVO_2). Blood gas tensions and pH were measured with an IL 1303 blood-gas analyzer and oxygen content was measured using an IL 282 cooximeter. Mean arterial blood pressure was measured continuously throughout the microsphere tests from the second femoral artery to ensure that blood pressure did not change appreciably. Heart rate was measured before each microsphere injection. At the end of the last microsphere test the rat was sacrificed and the brain was removed, sectioned into left and right cortical and subcortical samples, and weighed. The activity of each microsphere in brain and blood samples was analyzed using a Nuclear Chicago 1035 gamma counter and a Nuclear Data 600 multichannel analyzer. Cerebral blood flow was determined in each sample using the methods of Heymann et al. (4), but only cortical cerebral blood flow (CBF) is reported here. Cerebral oxygen consumption ($CMRO_2$) was calculated as the product of cortical CBF, corrected for brain weight, and cerebral arterial–venous blood O_2 content.

Drug and Reagents

Absolute ethanol 10% (vol/vol) in normal saline was used as the stock solution for all intraperitoneal injections. Midazolam maleate (RO 21-3981/1, Hoffman-LaRoche, Inc, Nutley, NJ) was dissolved in normal saline to a stock concentration of 0.2 mg/ml. A 3-carbo-*t*-butoxy-β-carboline (β-CCT) stock solution was prepared by dissolving the solid in a mixture of Emulphor EL-620P (Clay–Adams)–ethanol–normal saline (1:1:3) to a concentration of 0.4 mg/ml. Microspheres were

Table 1. Changes in Arterial Blood Pressure, Heart Rate, and Blood-Gas Tensions during Ethanol, Midazolam, and β-CCT Treatment

Treatment	*n*	Blood pressure (mm Hg)	Heart rate (beats/min)	Pa$\mathrm{CO_2}$ (mm Hg)	Pa$\mathrm{O_2}$ (mm Hg)	pH
Ethanol (mg/g)						
0	12	141 ± 2	342 ± 11	38.0 ± 0.3	117 ± 3	7.39 ± 0.02
0.75	10	126 ± 2^a	370 ± 4	37.7 ± 0.4	132 ± 7	7.37 ± 0.04
1.25	12	113 ± 3^a	408 ± 6^a	36.5 ± 0.4	125 ± 3	7.33 ± 0.03
2.50	11	97 ± 2^a	337 ± 7	35.8 ± 0.3	122 ± 3	7.38 ± 0.02
5.00	6	101 ± 2^a	350 ± 7	33.7 ± 0.3^a	146 ± 6^a	7.25 ± 0.06^a
Midazolam (mg/kg)						
0.57	13	116 ± 3^a	411 ± 4^a	36.8 ± 0.2	133 ± 3	7.39 ± 0.02
5.75	9	123 ± 3^a	376 ± 5	36.8 ± 0.3	123 ± 2	7.40 ± 0.03
β-CCT (mg/kg)						
Vehicle	9	150 ± 3	399 ± 4	35.9 ± 0.3	104 ± 3	7.41 ± 0.02
1.15	11	141 ± 2	439 ± 4	36.1 ± 0.3	153 ± 5	7.37 ± 0.04
Ethanol (2.5 mg/g) plus midazolam (0.57 mg/kg)	9	98 ± 3^a	400 ± 4^a	37.4 ± 0.5	184 ± 5	7.42 ± 0.02
Midazolam (0.57 mg/kg) plus β-CCT (1.15 mg/kg)	9	113 ± 2^a	397 ± 5	36.9 ± 0.4	204 ± 6	7.39 ± 0.02
Midazolam (5.75 mg/kg) plus β-CCT (1.15 mg/kg)	13	108 ± 2^a	386 ± 5	38.6 ± 0.4	218 ± 5	7.38 ± 0.04
Ethanol (2.5 mg/g) plus midazolam (0.57 mg/kg) plus β-CCT (1.15 mg/kg)	9	111 ± 2^a	358 ± 4^a	37.3 ± 0.3	159 ± 3	7.38 ± 0.03

[a] $P < 0.05$ compared to appropriate vehicle control.

suspended in normal saline solution with Tween-80 0.01% to a concentration of 500,000 microspheres/ml.

Blood ethanol levels were measured by placing 0.1-ml blood samples into 0.9-ml deionized water to lyse the red blood cells. One-microliter samples of this solution were injected directly onto a Teflon column (18 inches × 0.25 inches outer diameter) packed with Chromosorb P-AW-DMCS 60–80 mesh in a Packard gas chromatograph equipped with flame ionization detector. Operating conditions were performed from a modification of a previously described technique.

Statistical Methods

All data are reported as mean ± SEM. Statistical tests included analyses of variance to compare ethanol, midazolam, and β-CCT treatment effects, and unpaired *t*-tests to compare individual group differences.

Results

The mean values (± SEM) of mean arterial pressure (MAP), heart rate (HR), and arterial P$\mathrm{CO_2}$, P$\mathrm{O_2}$, and pH are summarized in Table 1. Although there were some significant differences in mean arterial pressure and pH, none of these were outside of the range of autoregulatory cerebrovascular function. Blood alcohol concentrations varied linearly with the intraperitoneally injected dose (Fig. 1). Small but significant increases were noted in CBF and CMR$\mathrm{O_2}$ with the 1.25 mg/g alcohol dose, and significant decreases in both parameters were seen with the 5.0 mg/g dose (Fig. 2). Neither cortical CBF nor CMR$\mathrm{O_2}$ were depressed 20 min after intraperitoneal injection of 2.5 mg/g ethanol, the dose chosen for investigating the effects of concomitantly administered midazolam and/or β-CCT. Midazolam produced 35–40% depression in cortical CBF and CMR$\mathrm{O_2}$ with both the 0.57 and 5.75 mg/kg doses (Fig. 3). The β-CCT infusion alone (1.15 mg/kg) produced a significant 30% increase in CMR$\mathrm{O_2}$ above the control levels without a significant change in cortical CBF (Fig. 3). And β-CCT reversed the depression in cortical CBF and CMR$\mathrm{O_2}$ produced by 0.57 but not 5.75 mg/kg midazolam. The effects of ethanol and midazolam given together are shown in Figure 4. Ethanol potentiated the 35–40% depression in cortical CBF and CMR$\mathrm{O_2}$ produced by 0.57 mg/kg midazolam, decreasing both variables approximately 70% from control. The β-CCT infusion (1.15 mg/kg) completely reversed the depression in cortical CBF and CMR$\mathrm{O_2}$ produced both by midazolam alone and midazolam plus ethanol.

Discussion

The interaction between ethanol and benzodiazepines has been studied by evaluation of psychophysical performance in humans (5) and by alterations in the be-

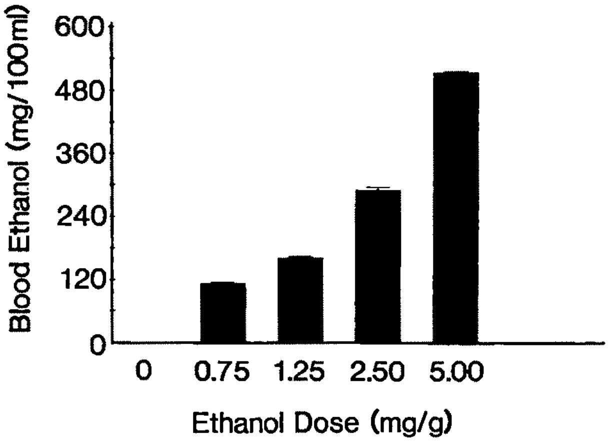

Figure 1. Blood ethanol concentrations 20 min after intraperitoneal ethanol injections (mean ± SEM). Number of samples in each group are given in Table 1. All values for ethanol doses were significantly greater than zero dose ($P < 0.01$).

havior of animals (6). These reports showed that the central sedative effects of diazepam were additive or supraadditive to those produced by alcohol. Physiologic measurements of this interaction are lacking, however. In the present studies we observed that ethanol potentiated the cerebrovascular and cerebral metabolic depression produced by midazolam. Ethanol, in concentrations that had little effect on cortical CBF or $CMRO_2$ alone, enhanced the central depressant effects of midazolam more than that affected by a 10-fold greater dose of the benzodiazepine. Our results also suggest that the potentiating effects of ethanol were produced by an effect at the benzodiazepine receptor because treatment with β-CCT, a benzodiazepine antagonist, reversed not only midazolam effects but also the interaction of midazolam plus ethanol.

The presence of high-affinity, saturable, and stereospecific binding sites for benzodiazepines in the mammalian CNS was first reported in 1977 (7,8). The correlation between the potencies of benzodiazepine compounds in displacing (H^3)-diazepam binding in vitro and their potencies as anxiolytics, anticonvulsants, and muscle relaxants strongly suggested that these binding sites were pharmacologic receptors (7–9). Benzodiazepine receptors appear relatively late in the phylogenetic scale, being first apparent in vertebrate species (10). In addition, their distribution within brain tissue is less dense in phylogenetically older brain regions, such as the pons and the medulla, than in newer areas such as the cortex (11). Central benzodiazepine receptors are located on neurons and are associated with synaptosomal contacts (12,13). Studies of the dissociation rates of radiolabeled benzodiazepines suggest the presence of two subtypes of receptor, referred to as type I and type II (14). These receptor subtypes also have a regional distribution, with type I receptors located in the cerebellum, globus pallidus, and lamina IV of the cortex, while type II receptors are found primarily in the caudate–putamen, dentate gyrus, and amygdala (15). The significance of the benzodiazepine receptor subtypes and their regional distribution is unknown at present, although they may mediate the separate pharmacologic functions of benzodiazepines (2). Biochemical analysis of benzodiazepine receptors suggests that they are physically, as well as functionally, associated with the γ-aminobutyric acid (GABA) receptor and the chloride ionophore (16). GABA acts at the benzodiazepine–GABA receptor–chloride ionophore complex by directly increasing conductance of the chloride ionophore and inhibiting the activity of the neuron. Benzodiazepines act at this complex by modulating the activity of the GABA receptor (17). The functional interaction of the receptor complex is indicated by the fact that the presence of both GABA

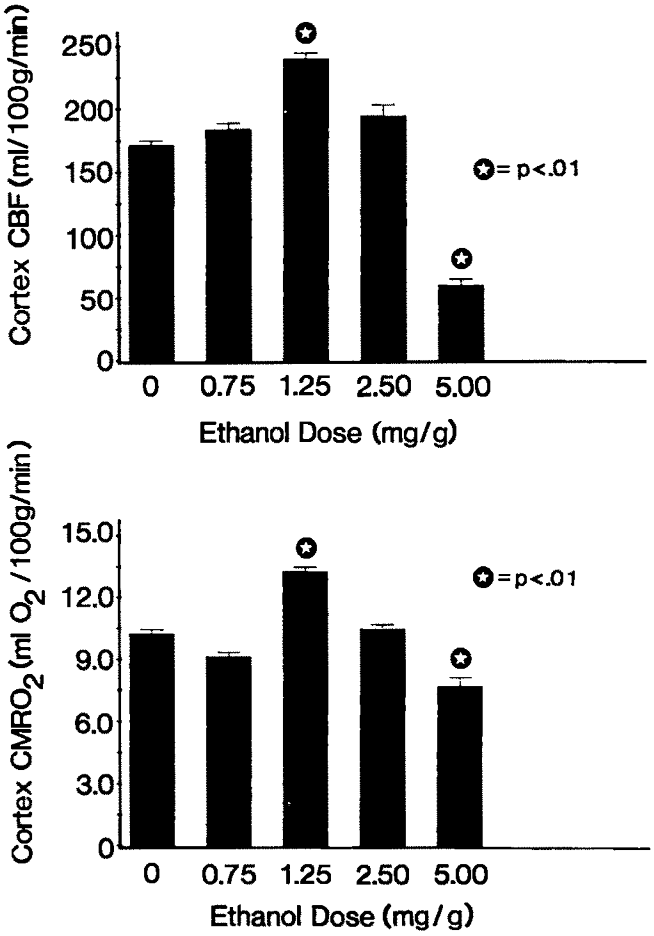

Figure 2. Cortical CBR and $CMRO_2$ changes during ethanol treatment. Number of animals and blood ethanol concentrations for each dose are shown in Table 1 and Figure 1, respectively. Each ethanol dose level was compared statistically to zero dose.

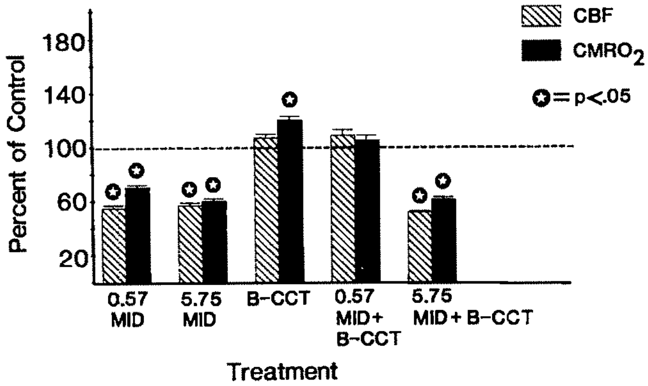

Figure 3. Cortical CBF and CMRO$_2$ changes produced by midazolam (MID) and β-CCT treatment. Dosage levels for midazolam represent mg/kg given over a 15-min infusion period. The β-CCT dosage was 1.15 mg/kg given over 15 min. Data are presented and compared statistically to the appropriate control for each test group and thus represent intragroup comparisons. Number of animals in each test group are given in Table 1. Data indicate a significant effect of β-CCT in reversing cortical CBF and CMRO$_2$ changes at 0.57 but not at 5.75 mg/kg midazolam doses ($P < 0.01$).

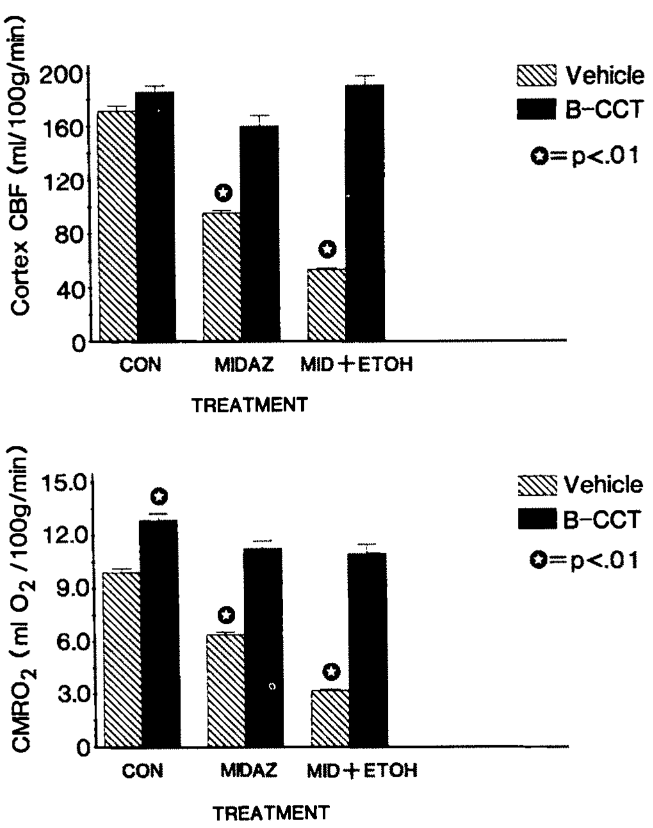

Figure 4. Cortical CBF and CMRO$_2$ changes during midazolam (MIDAZ or MID, 0.57 mg/kg intravenously), ethanol (ETOH, 2.5 mg/g intraperitoneally), and β-CCT (1.15 mg/kg intravenously) treatment. Number of animals in each group is given in Table 1. Control (CON) group received vehicle treatment for β-CCT. Each test group (solid bar) was compared statistically to vehicle-treated group (hatched bar) for each drug treatment.

and chloride ions can enhance the binding of (H^3)–diazepam to the benzodiazepine receptor (18). Ethanol also enhances (H^3)–benzodiazepine binding at concentrations between 10 and 100 nM, corresponding to plasma concentrations of 46–460 mg% (2,3). These effects are also consistent with the ability of ethanol to facilitate GABAergic-mediated inhibitor synaptic transmission (19). It is apparent that ethanol is capable of enhancing benzodiazepine-induced neuronal depression and facilitating the inhibitory action of the benzodiazepine–GABA receptor–chloride ionophore complex. While the molecular mechanism of this enhancement remains obscure, the results of our work with the benzodiazepine antagonist suggest that the ethanol effect is produced by a direct interaction with the benzodiazepine receptor.

Although these data suggest that ethanol potentiates the cerebral depressant effects of benzodiazepines by an interaction at the receptor level, there are other possible explanations for these results. It may be that ethanol and benzodiazepines produce their central depressant effect by different mechanisms or at separate sites of action. Under these conditions, benzodiazepines may act to unmask the metabolic depressant effects of ethanol, which are usually seen only with higher blood alcohol concentrations (> 300 mg%). If this were the case, the ability of β-CCT to reverse the enhanced midazolam–ethanol-induced cerebral metabolic depression would be indicative only of its ability to inhibit the action of midazolam and not of an interaction with ethanol at the receptor complex. This would be consistent with preliminary studies in which we have found an inability of β-CCT to reverse the behavioral depression produced by high doses of ethanol (unpublished results). This would suggest that separate depressor mechanisms are mediated by ethanol and benzodiazepine receptor stimulation that may interact at some level to facilitate depression. Another possible mechanism that has not been discussed is the possibility that ethanol or midazolam facilitated the action of the other by redistributing blood flow from cortical to subcortical regions and indirectly depressing metabolic activity. Although both cortical and subcortical blood flow were measured, only cortical blood flow was reported here. However, similar changes in flow were seen in cortical and subcortical regions under all treatment conditions. This suggests that an action of ethanol or midazolam to redistribute cerebral blood flow was not the primary mechanism of action.

Benzodiazepines have previously been shown to produce cerebrovascular and cerebral metabolic depression by other investigators. Carlsson et al. (20) showed that diazepam alone produced decreases in CBF in rats but no significant change in CMRO$_2$. Diazepam plus 70% N$_2$O–30% O$_2$ anesthesia produced a decrease in both CBF and CMRO_2 in these animals. They concluded that diazepam alone produced little cerebral metabolic depression and that N_2O potentiated the cerebral metabolic depression produced by the benzodiazepine. It is also possible that diazepam alone was not an adequate anesthetic and there was cerebral stimulation associated with the stress produced by the testing procedures. This is consistent with other reports that stress increases CBF and CMRO_2 (21). In N_2O-anesthetized dogs, Nugent et al. (22) reported that both diazepam and midazolam produced decreases in CBF and CMRO_2. They also found that midazolam produced greater cerebral depression at 5 min compared to 30 min after bolus intravenous injections, consistent with its short-acting effects. Intravenous infusions of midazolam were used in these studies to obtain a steady-state effect. We observed a depression in cortical CBF and CMRO_2 with midazolam that was similar between 0.57 and 5.75 mg/kg midazolam doses. This agrees with other reports that benzodiazepines produce a plateau of cerebrovascular and metabolic depression that occurs at low doses and is not greatly increased at higher doses (20). It is also consistent with the report that maximum behavioral effects of benzodiazepines are produced when a small number, less than 30% of central benzodiazepine receptors, are stimulated (2). The plateau of benzodiazepine effects as well as their high therapeutic index is probably related to the pharmacologic action of the benzodiazepine receptor, that of modulating GABA receptor effects within the benzodiazepine–GABA receptor–chloride ionophore complex.

The β-carbolines were first studied in an attempt to find an endogenous ligand for the benzodiazepine receptor. Neilsen et al. (23) isolated β-carboxylic-3-carbolytic acid ethyl ester (β-CCE) from human urine and determined it had a high affinity for benzodiazepine receptors. Although subsequent work showed that β-CCE was formed in the extraction and isolation procedures (24), β-carbolines have subsequently been found to be potent benzodiazepine antagonists. The β-carbolines have been shown to be active antagonists, not only by virtue of displacing benzodiazepines from their receptors but also by having intrinsic activity oppposite to that of benzodiazepines (25,26). The β-CCTs alone produced a significant increase in CMRO_2 above the levels seen in sham treated rats. The β-CCTs also reversed the cerebrovascular and cerebral metabolic depression produced by 0.57 but not 5.75 mg/kg midazolam. This indicates a dose-related reversal of midazolam effects with the benzodiazepine antagonist and approximate equipotence of midazolam and β-CCT at the benzodiazepine receptor.

It is apparent from these studies that the cerebrovascular and cerebral metabolic effects of midazolam are potentiated by ethanol. This occurs in spite of the fact that the dose of ethanol tested (2.5 mg/g intraperitoneally) produced no significant effect on cortical CBF or CMRO_2 alone. Our data also suggest that ethanol enhances the decrease in cortical CBF and CMRO_2 produced by midazolam by an interaction with the benzodiazepine–GABA receptor–chloride ionophore complex because this effect could be completely reversed by the benzodiazepine antagonist β-CCT. This is consistent with other reports that ethanol enhances benzodiazepine receptor binding and facilitates GABA-induced synaptic inhibition (3,19). It is also possible that ethanol produces cerebral depression by separate mechanisms that are facilitated in some way by benzodiazepines. Reversal of ethanol–benzodiazepine-induced cerebral depression by β-CCT would be consistent with this possibility. How these results relate to the behavioral depression of midazolam and ethanol is unknown. There may be some separation between the two because ethanol (0.75–5 mg/g) alone produced little metabolic, but marked behavioral, depression. Further studies will be required to determine how changes in CMRO_2 produced by benzodiazepines and alcohol relate to other physiologic and behavioral parameters.

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Hormonal and Hemodynamic Responses to Halothane and Enflurane in Spontaneously Hypertensive Rats

Edward D. Miller JR, MD, Judy J. Beckman, BS, and John S. Althaus, MS

MILLER ED, BECKMAN JJ, ALTHAUS JS. Hormonal and hemodynamic responses to halothane and enflurane in spontaneously hypertensive rats. Anesth Analg 1985;64:136–42.

Forty-two spontaneously hypertensive rats (SHR) and 42 normotensive Wistar–Kyoto rats (WKY) were anesthetized with either halothane or enflurane. Blood pressure, heart rate, cardiac output, distribution of blood flow, plasma renin activity, and plasma catecholamines were measured to determine in what manner the hypertensive animal responded to these two anesthetics. Major findings of the study were that plasma renin activity did not increase in the SHR despite a 25% reduction in MAP. The infusion of saralasin, an angiotensin II antagonist, resulted in a further decrease in blood pressure in SHR anesthetized with halothane but not with enflurane. Plasma catecholamine concentrations were elevated in the awake SHR and were decreased in SHR anesthetized with enflurane. Both halothane and enflurane anesthesia resulted in similar alterations in blood flow in the SHR. The normotensive WKY responded to halothane and enflurane in a different manner than the SHR. Plasma renin activity increased with the decrease in blood pressure with both agents. A further decrease in blood pressure occurred with saralasin infusion in WKY anesthetized with halothane or enflurane. Significant blood flow alterations occurred in the WKY anesthetized with both agents, but enflurane caused the greatest changes. The SHR may prove useful in examining the effects of anesthetic agents and other drugs so that we may have a better understanding of the perioperative management of the patient with essential hypertension.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane. BLOOD PRESSURE—hypertension. POLYPEPTIDES—renin–angiotensin. SYMPATHETIC NERVOUS SYSTEM—catecholamines.

A variety of clinical studies suggest that the hypertensive patient reacts to anesthetic agents in a manner that is dissimilar to normotensive patients (1,2). Most of these clinical studies have measured blood pressure and cardiac output during anesthesia and surgery, but these studies have been complicated by the use of induction agents and muscle relaxants, as well as the surgical procedure itself.

The spontaneously hypertensive rat (SHR) is thought to represent an acceptable model of essential hypertension in humans (3). Multiple studies have demonstrated that cardiovascular and hormonal responses to a variety of physiological maneuvers are similar to those known to occur in humans (4,5). We have used the SHR model to examine how anesthetic agents might affect organ systems while realizing the limitation of the SHR (6). The appropriate control for the study is one important aspect of the SHR studies. Most agree that because the SHR strain of rat was derived from the Wistar–Kyoto Rat (WKY), the appropriate normotensive control for the SHR is the WKY and not other strains of rat (7).

We compared the hemodynamic responses to halothane and enflurane anesthesia in both SHR and WKY. Not only did we measure blood pressure and heart rate, but also plasma catecholamine levels and arterial blood-gas tensions. The response of the renin–angiotensin system to anesthesia was also determined through the measurement of plasma renin activity and the infusion of saralasin, a competitive inhibitor of angiotensin II. The use of saralasin allows us to determine the importance of the renin–angiotensin system in blood pressure control (8). Because blood pressure alone does not allow for a determination of flow, we used the radioactive microsphere technique in an additional group of rats to measure total cardiac output and distribution of cardiac output. By using these various techniques we hoped to learn not only the responses of blood pressure in hypertension to these two anesthetics, but also

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Address correspondence to Dr. Miller, Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, VA 22908.

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Table 1. Mean Arterial Pressure and Heart Rate Response to Halothane or Enflurane Anesthesia

	Spontaneously hypertensive rat						Wistar-Kyoto rat					
	Control ($n = 8$)		Halothane ($n = 8$)		Enflurane ($n = (8)$)		Control ($n = 8$)		Halothane ($n = 8$)		Enflurane ($n = 8$)	
	MAP[b]	HR[c]	MAP	HR	MAP	HR	MAP	HR	MAP	HR	MAP	HR
Awake	153 ± 3	456 ± 14	168 ± 3	440 ± 8	181 ± 4	460 ± 6	123 ± 2	389 ± 15	126 ± 3	392 ± 12	124 ± 3	408 ± 10
Anesthetized	159 ± 2[a]	479 ± 13[a]	125 ± 4[a]	347 ± 9[a]	132 ± 6[a]	340 ± 10[a]	125 ± 3	383 ± 17	74 ± 2[a]	315 ± 8[a]	74 ± 2[a]	319 ± 10[a]
± Saralasin	162 ± 1	475 ± 12	107 ± 6[a]	325 ± 10[a]	124 ± 6	313 ± 8[a]	124 ± 4	375 ± 20	63 ± 3[a]	316 ± 8	70 ± 4[a]	299 ± 6[a]

[a] $P < 0.05$ by paired data.
[b] MAP expressed in mm Hg.
[c] HR expressed in beats/min.

the influence of these two agents on hormonal responses and, more importantly, on blood flow to various organs.

Methods

These studies were performed on 42 spontaneously hypertensive male rats (Charles River Laboratories) (mean weight 266 g, range 227–300 g) and 42 Wistar–Kyoto male rats (Charles River Laboratories) (mean weight 261 g, range 212–298 g) whose average age was 12–14 weeks. The rats were housed under identical conditions and provided with standard rat chow and water ad libitum until they were studied.

Two protocols were used to perform the studies. Forty-eight rats (24 SHR and 24 WKY) were studied to examine the hemodynamic and hormonal responses to two anesthetic agents. An additional 36 rats (18 SHR and 18 WKY) were studied using the radioactive microsphere technique. Ideally, experiments examining hemodynamic and hormonal responses should be done in the same animal; however, the requirement for blood sampling and the derangement this could cause necessitated the use of different groups of animals.

Forty-eight rats (24 SHR and 24 WKY) were briefly anesthetized with diethyl ether delivered via a nose cone, and a femoral artery and vein were cannulated (PE-50 tubing). The cannulae were exteriorized and flushed with a solution of heparin and physiologic saline. The rats were placed in restraining cages (Braintree Scientific Inc.) for at least one hour to allow recovery from anesthesia. Blood pressure, which was monitored continuously through the arterial cannula by a Statham P23Db pressure transducer using a Brush Mark 2400 recorder, had stabilized well before the end of the recovery period, and the animals were awake and alert. The protocol consisted of a 1-hr awake period, a 20-min anesthetic induction period, 60 min of anesthesia, and a 30-min infusion of saralasin. Anesthesia was established with either 1.3 vol% halothane (SHR $n = 8$, WKY $n = 8$) or 2.2 vol% enflurane (SHR $n = 8$, WKY $n = 8$). These values represent approximately equipotent anesthetic concentrations in young rats (9,10). A control group (SHR $n = 8$, WKY $n = 8$) was treated identically but remained unanesthetized throughout. All animals breathed room air spontaneously throughout the experiment. All animals were placed under a heating lamp to maintain rectal temperature at 37°C.

To ensure a large excess of saralasin relative to angiotensin II at the angiotensin-binding sites, an initial dose of saralasin, 100 μg/kg, dissolved in 0.9% saline solution (approximately 150 μg/ml) was infused intravenously, and the infusion was maintained at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the next 30 min (11). The volume of saralasin administered did not exceed 0.8 ml.

Arterial blood (0.5 ml) for determination of plasma renin activity (PRA) was obtained immediately prior to anesthesia. After 1 hr of stable anesthesia or after 1 hr of being awake for the control group, 1.5 ml of blood was obtained for determination of PRA and plasma catecholamines. A third arterial blood sample was obtained at the end of the infusion for determination of PRA and plasma catecholamines. The removed blood, placed in vials containing EDTA, was centrifuged; the plasma was withdrawn; and the red blood cells were suspended in an equal volume of saline solution and administered intravenously to replace the shed blood. Catheters were flushed periodically with normal saline to ensure accurate blood pressure measurements. PRA was estimated using 0.2 ml plasma instead of 1 ml plasma, as is described by Haber et al. (12), using New England Nuclear reagents. The plasma was incubated for two hours to generate angiotensin I, which was estimated by ra-

Table 2. Plasma Renin Activity (ng·ml^{-1}·hr^{-1})

	SHR			WKY		
	Control ($n = 8$)	Halothane ($n = 8$)	Enflurane ($n = 8$)	Control ($n = 8$)	Halothane ($n = 8$)	Enflurane ($n = 8$)
Awake	2.2 ± 0.7	1.9 ± 0.2	2.5 ± 0.7	2.2 ± 0.6	2.9 ± 0.6	2.2 ± 0.2
Anesthetized	1.4 ± 0.6	1.6 ± 0.4	1.3 ± 0.2	1.4 ± 0.2	13.4 ± 3.6[a]	4.8 ± 0.9[a]
± Saralasin	2.0 ± 0.7	10.1 ± 2.6[a]	4.1 ± 1.2[a]	7.5 ± 5.8	83.0 ± 7.3[a]	54.8 ± 17.0[a]

[a] $P < 0.05$ by paired data.

dioimmunoassay, and the renin activity calculated as ng·ml^{-1}·hr^{-1}. The plasma samples from the six groups were assayed randomly in ten separate renin assays. Standard curves for each assay were done in triplicate, and all samples were assayed in duplicate. Renin values that exceeded the standard curve values were diluted and reassayed.

Blood samples for analysis of catecholamines were collected in iced polystyrene tubes containing EDTA. After centrifugation, 550 μl of plasma was collected and stored at −80°C for later analysis. Catecholamines were extracted 1–10 days later and then assayed by high-performance liquid chromatography. Briefly, 8 pmol of internal standard (3,4,dihydroxybenzylamine) were added to 500 μl of plasma, and the catecholamines were absorbed to alumina under alkaline conditions. The catecholamines then were eluted with 250 μl of 0.1N perchloric acid. Thereafter, 200 μl of the eluate was injected into the chromatography and separated by an ODS 5-μm reverse phase column. Catecholamines were detected electrochemically with a 30-pg sensitivity threshold (13). There was less than a 5% error in repeated determinations of samples containing 100–200 pg/ml of catecholamines.

To assess the influence of anesthetic agents on cardiac output and distribution of blood flow, 36 additional rats were studied (18 SHR and 18 WKY). The rats were anesthetized either with halothane (1.3%) or enflurane (2.2%), and PE-50 polyethylene tubing was passed into the left ventricle using pressure monitoring to verify location. The neck incision was closed, and a femoral artery was cannulated with PE-50 tubing. Catheters were flushed with a solution of heparin and physiologic saline solution. Blood pressure was monitored as previously described.

The protocol consisted of a 1-hr period of stable anesthesia after the surgical preparation. This time was adjusted to resemble closely the protocol of the previously described rats. Anesthesia consisted of 1.3% halothane in air (SHR $n = 8$, WKY $n = 8$) or 2.2% enflurane in air (SHR $n = 10$, WKY $n = 8$). After 1 hr of stable anesthesia, arterial blood (0.2 ml) was withdrawn for determination of arterial blood-gas tensions.

To determine cardiac output and distribution of blood flow, carbonized microspheres were injected (14). Strontium-85 labeled microspheres (15 ± 1.1 μm) with specific activity of 9.6 mCi/g were used. These were suspended in 10% dextran containing 0.05% Tween 80 and counted in a gamma counter (LKB 1282 Compugamma). After initial counting, the microspheres were agitated again, 0.1–0.2 ml (40,000–60,000 microspheres) was injected into the left ventricular catheter over 5 sec, and the catheter was flushed with 0.4 ml saline solution. Blood was withdrawn from the femoral artery by a constant withdrawal pump for 10 sec prior to 40 sec after the microsphere injection. The blood was then placed in a preweighted counting vial, and the actual withdrawal rate (approximately 0.76 ml/min) was determined by weighing the vial. The empty injection syringe again was counted to determine any residual microspheres not injected. Microspheres were injected at the end of the 1 hr of stable anesthesia; then the rats were killed by injection of potassium chloride through the ventricular catheter and the organs were removed, weighed, and placed in counting vials. The position of the left ventricular catheter was verified by direct vision. Samples of skin, muscle, liver, and small intestine were taken; otherwise, the whole organ was counted. Total weights of the liver and small intestine were determined for each animal. Tissue and blood samples then were counted for 5 min in a gamma counter at the appropriate energy spectrum.

Cardiac output was determined by the reference sample method (cardiac output = counts injected × reference sample withdrawal rate ÷ reference blood counts). Regional distribution of cardiac output was calculated by comparing the radioactivity in each organ with the total injected radioactivity. Organ flow was determined by multiplying the cardiac output by the fractional distribution of the cardiac output to the organ.

Data are presented as the mean values ± SEM. Student's t-test for paired data was used when ap-

Table 3. Plasma Catecholamines

	SHR						WKY					
	Control (n = 7)		Halothane (n = 7)		Enflurane (n = 8)		Control (n = 7)		Halothane (n = 7)		Enflurane (n = 8)	
	NE[a]	EPI[b]	NE	EPI	NE	EPI	NE	EPI	NE	EPI	NE	EPI
Treatment	621 ± 89	512 ± 109	666 ± 178	269 ± 76	256 ± 60[c]	325 ± 84	274 ± 50[d]	382 ± 54	168 ± 32	200 ± 33	119 ± 49	128 ± 25[c]
+ Saralasin	384 ± 41	316 ± 86	756 ± 154	322 ± 51	301 ± 78[c]	419 ± 76	588 ± 122[c]	500 ± 222	279 ± 123	286 ± 52	106 ± 18[c]	232 ± 48

[a] NE, norepinephrine expressed in pg/ml.
[b] EPI, epinephrine expressed in pg/ml.
[c] $P < 0.05$ compared to awake.
[d] $P < 0.05$ awake SHR vs awake WKY.

propriate. Statistical significance of other data was determined by one-way analysis of variance. $P < 0.05$ was considered significant.

Results

Mean arterial pressure (MAP) in the SHR was 159 ± 2 mm Hg during the pretreatment period. After stable anesthesia with halothane and enflurane, MAP decreased to 125 ± 4 mm Hg and to 132 ± 6 mm Hg ($P < 0.05$), respectively. With the infusion of saralasin, MAP did not change in the control group or in those anesthetized with enflurane. In contrast, in SHR anesthetized with halothane, a significant decrease in MAP occurred (107 ± 6 mm Hg) (Table 1).

Mean arterial blood pressure in the WKY was 125 ± 3 mm Hg during the pretreatment period. After 1 hr of stable anesthesia with halothane, MAP had decreased to 74 ± 2 mm Hg ($P < 0.05$). Similarly, enflurane anesthesia also resulted in a decrease in MAP to 74 ± 2 mm Hg. The infusion of saralasin in the unanesthetized WKY did not alter MAP. In contrast, saralasin decreased MAP significantly in rats anesthetized with halothane or enflurane (63 ± 3 mm Hg, 70 ± 4 mm Hg, respectively) (Table 1).

Heart rate was significantly slower in awake WKY than in awake SHR (383 ± 17 vs 479 ± 13 beats/min). Anesthesia with halothane and enflurane decreased heart rate in both the SHR and WKY. The infusion of saralasin further decreased heart rate in all anesthetized animals except WKY anesthetized with halothane (Table 1).

PRA during the pretreatment period was similar in both SHR and WKY. With halothane and enflurane anesthesia in the SHR, no increase in PRA could be observed. In contrast, WKY anesthetized with either halothane or enflurane did demonstrate increases. The infusion of saralasin resulted in increases in PRA in the WKY and SHR anesthetized with halothane and enflurane (Table 2).

Plasma norepinephrine and epinephrine were significantly greater in the SHR as compared with the WKY. Enflurane anesthesia resulted in a decrease in norepinephrine when compared to the awake state in SHR. No such decrease was seen in SHR anesthetized with halothane. The WKY also demonstrated a decrease in plasma epinephrine when enflurane anesthesia was administered. The infusion of saralasin in the WKY during the awake period resulted in a significant increase in plasma norepinephrine (Table 3).

Cardiac output was similar in both SHR and WKY anesthetized with halothane (57 ± 5 ml/min and 59 ± 3 ml/min, respectively; cardiac index 226 ± 24 ml and 235 ± 14 ml/min, respectively). A decrease in small bowel blood flow was found in the SHR compared to WKY, although there were small increases in skin and muscle blood flow in the SHR (Fig. 1).

Cardiac output in WKY anesthetized with enflurane was 75 ± 4 ml/min (cardiac index 306 ± 16 ml/min); and in SHR anesthetized with enflurane, 67 ± 3 ml/min (cardiac index 268 ± 11 ml/min). Although similar cardiac output was found, there were marked differences in blood flow to various organs. Decreases in blood flow to brain, lung (bronchial flow), left kidney, and small bowel were found in SHR anesthetized with enflurane as compared to WKY; whereas increases in blood flow to heart, skin, and muscle were observed in SHR as compared to WKY (Fig. 2).

Arterial blood-gas analysis done at the end of the microsphere injection showed that the WKY anesthetized with halothane were hypoxic. Arterial oxygen was greater than 60 mm Hg in the other groups of rats. SHR had lower carbon dioxide tension than did WKY when anesthetized with either halothane or enflurane (Table 4).

Discussion

The spontaneously hypertensive rats maintained elevated mean arterial pressure throughout the experiment. The awake control group demonstrated that

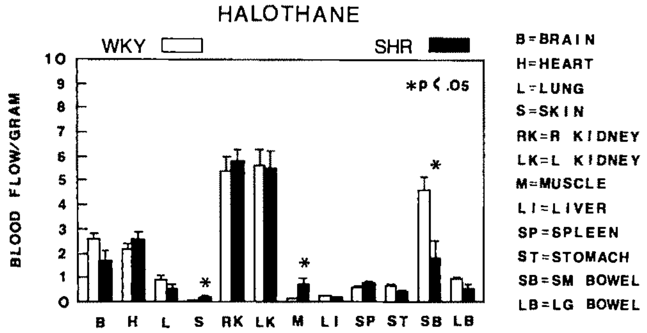

Figure 1. Blood flow (ml/min) per gram of tissue in normotensive WKY and hypertensive SHR with 1 MAC halothane anesthesia. $^*P < 0.05$ by analysis of variance.

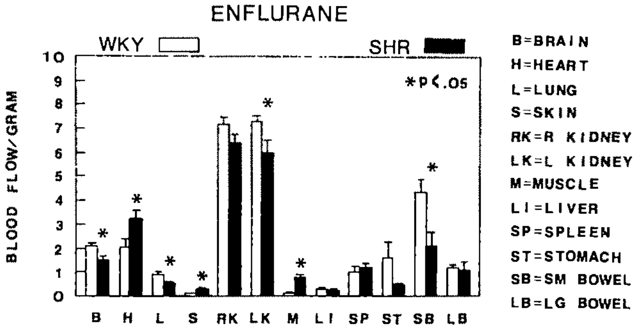

Figure 2. Blood flow (ml/min) per gram of tissue in normotensive WKY and hypertensive SHR with 1 MAC enflurane anesthesia. $^*P < 0.05$ by analysis of variance.

these animals are sensitive to external stimuli because by the end of the second hour in the restraining cage, both mean arterial pressure and heart rate had increased slightly. Further support of these data is the elevated plasma catecholamine levels seen in the awake SHR. Kopin et al. (15) likewise observed that the SHR had exaggerated responses to stress as demonstrated by elevated concentrations of plasma catecholamines. This exaggerated response to stress also appears to occur in humans with essential hypertension (16).

Both halothane and enflurane decreased mean arterial pressure approximately 25% in the SHR. Because cardiac output was similar with both anesthetic agents, the overall effect on total peripheral resistance was similar. This is demonstrated graphically in Figure 3, where blood flow to various organs is plotted with each agent in the SHR. Except for the spleen, blood flow to the various organs in the SHR was similar with both agents. These data suggest no specific advantage of one agent over the other in this type of hypertension.

Although minimal effects of halothane or enflurane could not be demonstrated on distribution of blood flow in the SHR, such is not true in the normotensive WKY. In the WKY, halothane and enflurane resulted in differences in flow to skin, muscle, and kidney. In each of these organs, blood flow was greater with enflurane than with halothane (Fig. 4). Enflurane's more profound influence on peripheral resistance was also demonstrated in our previous report on normotensive Wistar rats (14). When one compares the blood flow to various organs in the WKY and SHR with one agent, differences are seen more readily. Halothane anesthesia results in small increases in blood flow to skin and muscle in the SHR (Fig. 1). Enflurane, in contrast, results in increases in blood flow to heart, skin, and muscle; and results in decreases in blood flow to the brain, lung (bronchial), kidney, and small bowel. Whether these alterations in distribution of blood flow are detrimental to organ function was not investigated in this study. Both agents increased blood flow to skin and muscle, which may represent an inappropriate distribution of blood flow to nonvital organs, similar to what we have reported in rats with renovascular hypertension (17).

The effects of halothane and enflurane on the arterial pressure of the normotensive WKY were similar to those observed in SHR, but more profound. With similar MAC concentrations of halothane and enflurane, MAP decreased 40% in the WKY and only 25% in the SHR. Cardiac output was more significantly depressed with halothane than with enflurane, a finding that agrees with our previous reports on normotensive Wistar rats and humans (17,18). Because blood pressure decreased a similar degree with halothane and enflurane, but cardiac output was different, the effect of enflurane was to increase blood flow to the skin, muscle, and kidney.

The response of the renin–angiotensin system to halothane or enflurane anesthesia was also dissimilar in the SHR and WKY. Although PRA was similar in both strains of awake rats, halothane and enflurane caused an increase in PRA in WKY only, the response being the greatest in WKY anesthetized with halothane. The increase in PRA most likely results from the decrease in mean arterial pressure seen with halothane. A similar decrease in pressure with enflurane, however, did not result in as large an increase in PRA. This difference between halothane and enflurane on renin release has been noted before (17).

That the plasma renin response is an important factor in blood pressure support is demonstrated by the data obtained with saralasin, the angiotensin II antagonist. A significant decrease in MAP was seen with saralasin in WKY anesthetized with either agent, an expected finding with the elevation of PRA. The decrease in MAP in SHR anesthetized with halothane and enflurane, however, did not result in an increase in PRA. This would suggest that decreasing blood pressure in hypertensive rats by potent inhalational

Table 4. Arterial Blood Gases in SHR and WKY Breathing Room Air Plus Agent

	SHR				WKY			
	n	Po_2	Pco_2	pH	*n*	Po_2	Pco_2	pH
Halothane	8	71.4 ± 4.8	27.4 ± 2.0	7.38 ± 0.02	10	48.5 ± 1.1	39.3 ± 1.3	7.34 ± 0.01
Enflurane	10	65.2 ± 2.8	26.2 ± 1.5	7.40 ± 0.02	8	63.8 ± 3.5	33.3 ± 2.3	7.44 ± 0.02

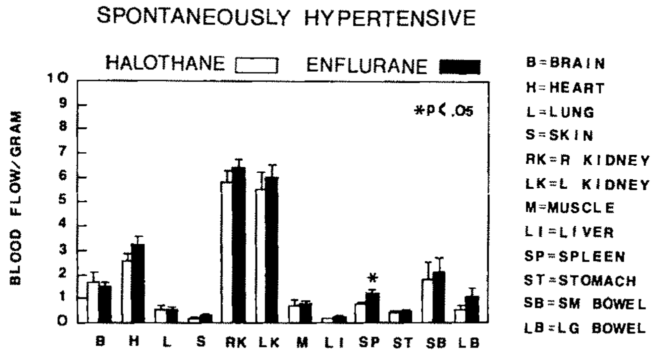

Figure 3. Blood flow (ml/min) per gram of tissue in hypertensive SHR with 1 MAC halothane or enflurane anesthesia. $^*P < 0.05$ by analysis of variance.

agents does not activate the various mechanisms responsible for renin release from the kidney (19). However, renin is known to exist in vascular smooth muscle as well as within the brain, areas not examined by the measurement of plasma renin activity (20,21). That angiotensin II is important in blood pressure control in the SHR anesthetized with halothane is well demonstrated by the decrease in MAP with the saralasin infusion. A tendency for MAP to decrease with saralasin was also seen with enflurane, but to a much lesser extent. This most likely represents the more profound effect of enflurane on peripheral resistance so that angiotensin II is relatively ineffective.

A very similar degree of activity is seen in the renin–angiotensin system in the awake state in both WKY and SHR. Not only was PRA similar, but the response to saralasin did not result in significant changes in heart rate or blood pressure. Once alterations in blood pressure are caused by potent inhalational agents, significant differences between WKY and SHR are seen. First, the plasma renin response is greater in the WKY and the negative feedback loop is easily identified (22). The SHR does not show these same characteristics. The data demonstrate that the measurement of PRA is a poor indicator of the degree of blood pressure support when potent inhalational agents are used to decrease blood pressure. Whether the saralasin is acting only on peripheral vascular smooth muscle directly or on other sites cannot be determined in this study. However, the response to saralasin in the SHR anesthetized with halothane could not have been predicted from the measurement of plasma renin activity alone.

Certainly, other mechanisms are also known to support blood pressure and, therefore, we attempted to quantitate the importance of the sympathetic nervous system in these two strains of rats through the measurement of plasma catecholamine levels. Our data show that the norepinephrine levels in awake SHR are elevated compared with those of the awake WKY. The infusion of saralasin in the WKY resulted in an increase in catecholamines, which agrees with a known property of saralasin to stimulate catecholamine release (23). Such an increase in catecholamines to saralasin was not found in the SHR. There was a tendency for halothane to decrease plasma catecholamine levels except in the SHR anesthetized with halothane. However, there was a much greater variability in the data obtained in the SHR than the WKY, suggesting that sympathetic nervous system activity is at a much higher degree. This may explain why no further increase in catecholamine levels in SHR was seen with saralasin. It should be noted that the WKY anesthetized with halothane, in whom the arterial oxygenation was the poorest, showed no evidence of increased sympathetic nervous system activity. Certainly, hypoxia alone is known to stimulate the catecholamine response (24). Whether the catecholamine response itself is blocked by halothane or the stimulus was too weak was not examined in this study.

The relative hypoxia seen in WKY anesthetized with halothane may have influenced our results. We were interested in examining only the anesthetic agent and not the effects of changes in arterial Po_2. When one examines blood pressure, heart rate, and catecholamine responses to halothane or enflurane, similar results are found. The only difference seen is a slightly greater response in plasma renin activity and a lower cardiac output in WKY anesthetized with halothane.

It would appear that the hypoxia did not result in significant changes in the variables measured and was unlikely to have altered our results. The fact that the arterial oxygenation was greater in the SHR than the WKY, suggests that the lower blood pressure and lower cardic output in the WKY anesthetized with halothane were the major determinants of the arterial oxygenation.

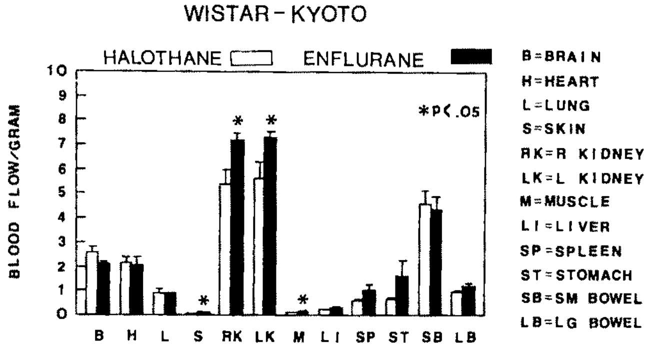

Figure 4. Blood flow (ml/min) per gram of tissue in normotensive WKY with 1 MAC halothane or enflurane anesthesia. $^*P < 0.05$ by analysis of variance.

In summary, halothane and enflurane anesthesia in spontaneous hypertensive rats results in predictable changes in blood pressure and heart rate. The importance of the renin–angiotensin system in blood pressure control cannot be established through the measurement of plasma renin activity. Sympathetic nervous system activity as measured by plasma catecholamine concentrations had a tendency to be reduced by both anesthetics except in SHR anesthetized with halothane. Distribution of blood flow to various organs is more affected by enflurane than by halothane when the normotensive WKY is used as the control. There was no evidence that major alterations in flow to any organ occurred, but individual organ function was not tested. Both halothane and enflurane anesthesia showed similar patterns of blood flow distribution in the spontaneously hypertensive rat. The present experiments support the hypothesis that the SHR is an acceptable model for use in investigations of the effects of anesthetic agents and other drugs in order to have a better understanding of how to care for the patient with essential hypertension in the perioperative period.

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Review Article

Principles of Neuroanesthesia for the Nonneurosurgical Patient with CNS Pathophysiology

Joseph M. Messick, JR, MD, Leslie A. Newberg, MD, Michael Nugent, MD, and Ronald J. Faust, MD

Prevention of neuronal damage is essential in the anesthetic management of all patients. Awareness of the importance of neuronal preservation is heightened in patients with underlying central nervous system pathophysiology, whether or not the operative procedure involves the brain or the spinal cord.

Neurons perform the primary function of the brain and spinal cord—transmission of nerve impulses (1,2). This electrical function is intimately related both to perfusion and to cerebral metabolism, which involves aerobic oxidation of glucose (3). Because of inadequate primary substrate stores (oxygen and glucose), neurons of the brain and spinal cord are highly dependent upon vascular perfusion for minute-to-minute delivery of these substrates (2,4–6). Oxygen (O_2) delivery inadequate for O_2 demand causes neuronal hypoxia (defined as neuronal PO_2 below a critical level), which can produce cell damage. Because neurons regenerate poorly, damage to these cells can be irreversible.

Neuronal hypoxia usually results from decreased O_2 delivery rather than increased O_2 consumption (7). Reduced O_2 delivery may be due to hypoxemia (decreased arterial O_2 content, with an adequate cerebral blood flow), or to ischemia (pathologic decrease in cerebral blood flow, with no deficit in arterial O_2 content) (7). The pathophysiology and treatment are different for these two causes of reduced O_2 delivery.

This article addresses principles of neuroanesthesia designed to prevent neuronal hypoxia secondary to ischemia. An abbreviated review of cerebral metabolism, cerebral perfusion, and intracranial pressure (ICP) is followed by discussions of the application of principles of neuroanesthesia to patients who have cerebrovascular disease, increased (or the potential for increased) ICP, or increased risk of spinal cord ischemia. We review current information regarding brain protection and conclude with some remarks addressing the management of the trauma patient from the neuroanesthesia perspective.

Cerebral Metabolism

The characteristic features of neuronal metabolism are high cellular energy demands utilizing adenosine triphosphate (ATP) energy obtained from obligatory aerobic glucose oxidation, no (O_2) or minimal (glucose, glycogen) substrate reserves relative to consumption rates, and low concentrations of high energy phosphate compounds (1,2,6). These characteristics render the brain highly dependent upon its circulation for minute-to-minute supply of its primary substrates, O_2, and glucose (2,4,6,7).

CMRO_2

Published values for the cerebral metabolic oxygen consumption rate ($CMRO_2$) of the normal human brain range from 2.9 to 4.0 ml of O_2 per 100 g of brain per min, with 3.3–3.5 (or approximately 50 ml/min in the 1400-g brain of adult humans) representing an average value (4). $CMRO_2$ values are greater in children, approximating 5 ml $O_2 \cdot (100\ g)^{-1} \cdot min^{-1}$ in the middle of the first decade of life (4,5). $CMRO_2$ has two components. The majority (50–60% or more) of $CMRO_2$ subserves neuronal function, whereas a lesser portion is required for maintenance of cellular integrity (7).

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Address correspondence to Dr. Messick, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

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CMR$_{glucose}$

Glucose, the other essential cerebral substrate, is transported from blood to brain by a stereospecific carrier-mediated transport mechanism (1) in which the role of insulin is controversial (1). At normal concentrations of blood glucose, glucose transport is not the limiting factor for cerebral metabolism (1). Rather, because cerebral glucose (and glycogen) stores exceed cerebral O_2 stores, O_2 deficiency and not glucose deficiency causes loss of consciousness if cerebral circulation suddenly ceases (5,6). The normal cerebral metabolic rate for glucose ($CMR_{glucose}$) approximates 4.5 mg·(100 g)$^{-1}$·min^{-1} (8). Anesthesia appears to alter cerebral glucose transport by altering the cerebral metabolic rate and not by having a direct effect on the transport mechanism (1).

Studies suggest that $CMRo_2$ and $CMR_{glucose}$ decline by approximately 6–9% and 23%, respectively, in physically and mentally healthy elderly subjects, with no reduction in cerebral blood flow (CBF) (9).

Effect of CO_2 on Cerebral Metabolism

$CMRo_2$ values do not change significantly with either elevated $Paco_2$ (to a $Paco_2$ of 80 mm Hg in dogs (10), 51 mm Hg in humans (11)) or decreased $Paco_2$ (25 mm Hg in humans (11)), although the ratio of $CMRo_2$ to $CMR_{glucose}$ changes at either extreme (10–12). Subsequent studies have shown that hypercapnia is accompanied by a decrease in $CMR_{glucose}$ (11,12).

Healthy adult male volunteers anesthetized with a thiopental (5 mg/kg)–70:30 nitrous oxide/oxygen mixture–curare technique had decreased aerobic and increased anaerobic cerebral metabolism during hypocapnia ($Paco_2 < 20$ mm Hg) (13). Possible mechanisms suggested by the authors included CBF decreased below a "critical" level, decreased O_2 transfer due to respiratory alkalosis, a specific effect of hypocapnia or alkalosis on cerebral metabolism, and a combination of these mechanisms. Note that in the presence of increased cerebral metabolic requirements or of compromised cerebral perfusion (or of both), relative hypocapnia at a $Paco_2$ greater than 20 mm Hg (or higher comparable levels in patients with chronic hypercapnia) could produce more anaerobic cerebral metabolism.

Seizures

Hypermetabolic states such as epileptiform activity greatly increase neuronal O_2 demand.

Ischemia

Ischemia results when blood flow is inadequate for the metabolic demands of the tissue and includes inadequate delivery of O_2 and other substrates, inadequate removal of CO_2, and increased production of lactic acid secondary to a shift from aerobic to anaerobic metabolism. Large reductions in perfusion can be tolerated if the tissues can increase their O_2 extraction from the blood sufficiently to meet O_2 demands (14). When maximum O_2 extraction is reached, however, further decreases in perfusion result in ischemia.

Cerebral[1] ischemia may be subdivided into complete and incomplete ischemia. In complete ischemia (that is, cerebral circulatory arrest) there is rapid depletion of high-energy phosphates, failure of membrane ion pumps (leading to potassium ion efflux and influx of sodium, water, and chloride ions), and membrane depolarization (15). Irreversible cell damage may occur within minutes if corrective measures are not taken. In incomplete ischemia, the outcome largely depends on residual perfusion and O_2 supply relative to O_2 demand (15). With the exception of the ischemia associated with cardiac arrest, it is incomplete ischemia with which the anesthesiologist deals and upon which we will focus.

Critical Cerebral Blood Flow

The CBF below which cerebral ischemia occurs has been termed the critical CBF. As noted earlier, O_2 availability rather than blood flow per se is the essential element for tissue function. Because brain stores of O_2 and glucose are minimal, however, perfusion is critical for maintenance of neuronal function. As CBF decreases, a flow level is reached above which cortical electrical function is sustained and below which it is abolished. This threshold of electrical failure occurs in humans at hemispheric flow rates of 16–17 ml·(100 g)$^{-1}$·min^{-1} (15). In baboons, cortical evoked somatosensory potentials are abolished at local flow rates below approximately 15 ml·(100 g)$^{-1}$·min^{-1} (15). Using the electroencephalogram (EEG) as a monitor of cortical activity,[2] Sharbrough et al. (16) found EEG evidence of ischemia when regional CBF (rCBF) (middle cerebral artery distribution) was less than 18 ml·(100 g)$^{-1}$·min^{-1} during halothane–N_2O:O_2 anesthesia in normocapnic patients undergoing carotid endarterectomy. No EEG evidence of ischemia occurred at rCBF > 24 ml·(100 g)$^{-1}$·min^{-1}. In a review of 1145 carotid endarterectomies performed during general anesthesia (halothane or enflurane–N_2O:O_2) and normocapnia, EEG changes correlated well with reduction in rCBF below the critical flow (defined as the rCBF required to maintain a normal EEG) (17). Because EEG changes invariably occurred at rCBF < 10 ml·(100 g)$^{-1}$·min^{-1}, usually occurred at rCBF < 15, and never occurred at rCBF > 24, the authors concluded that, during normocapnia and general anesthesia with halothane or enflurane, critical rCBF is approximately 15 ml·(100 g)$^{-1}$·min^{-1} (17).[3]

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[1] The same principles apply to neurons whether they are in the brain or the spinal cord.

[2] The EEG has proved to be a reliable indicator of cortical function and hence of cortical ischemia during appropriate levels of general anesthesia and $Paco_2$ (16,17).

At the threshold of electrical failure, cerebral energy stores approximate normal levels, and potassium ion concentration ([K$^+$]) in the extracellular fluid (ECF) is normal or only slightly elevated, although the rate of ion pumping already is affected (15).

As CBF declines further, a threshold of energy failure and ion pump failure is reached, below which there is massive efflux of K$^+$ from damaged cells (15) and an influx of calcium. This critical threshold occurs at a CBF of approximately 10 ml·(100 g)$^{-1}$·min^{-1} in the baboon. The ischemic brain between the two thresholds may be characterized by electrical silence, normal or slightly elevated ECF [K$^+$], and moderate energy failure, which, however, does not result in neuronal damage (15). Such tissue forms a ring (the penumbra) around the densely ischemic center of focal ischemia (15). Because the penumbra contains viable brain tissue, measures that maintain or improve perfusion, stabilize membranes, or reduce energy needs may be critical in terms of outcome (15). Autoregulation (see the autoregulation section below) is lost in this area, and perfusion is passively dependent on cerebral perfusion pressure (CPP). Hypotension must be avoided. Induction of the inverse-steal phenomenon (see the CBF regulation section below) has been advocated by some (15) to promote flow in the region of vasomotor paralysis.

Cerebral Circulation

Anatomy

Two general types of arteries supply the cerebral hemispheres: conducting vessels and penetrating vessels (18). Conducting arteries essentially are nonresistance vessels that include the carotid, middle cerebral, anterior cerebral, vertebral, basilar, and posterior cerebral arteries, together with their major and minor branches (17,18). These vessels provide adequate perfusion pressure to the resistance vessels—the penetrating or nutrient arterioles that enter the brain parenchyma at right angles to the surface vessels and are the site of primary autoregulation of CBF (18). Although both the conducting vessels and the parenchymal microvasculature receive autonomic innervation, the functional roles of autonomic control have not been delineated (19–21). Neurogenic tone is not essential to normal CBF regulation. Maximal sympathetic nerve stimulation produces only a reduction of 5–10% in CBF; a similarly moderate vasodilator response follows maximal parasympathetic stimulation. Neurogenic control, however, may be important in regulating cerebrovascular volume and thus, indirectly, ICP (19).

The thin-walled, valveless cerebral veins drain into relatively thick-walled dural sinuses. The site of entry of a cerebral vein into a dural sinus anatomically presents a relatively fixed orifice and physiologically presents a significant resistance to flow. Because cerebral venous pressure must slightly exceed cerebrospinal fluid (CSF) pressure for venous blood to flow, pressure in the intracerebral veins must be higher than that in either the dural sinuses or the internal jugular vein bulb (20). When calculating CPP, therefore, mean ICP, the best approximation of true intracranial cerebral venous pressure, is subtracted from mean arterial pressure (MAP): $\mathrm{CPP} = \mathrm{MAP} - \overline{\mathrm{ICP}}$.

Cerebral Blood Flow

CBF is directly proportional to CPP and inversely proportional to cerebrovascular resistance (CVR): $\mathrm{CBF} = (\mathrm{MAP} - \overline{\mathrm{ICP}})/\mathrm{CVR}$. The primary component of CVR is vessel diameter. Blood viscosity is a secondary component.

Normal human CBF is 45–60 ml·(100 g)$^{-1}$·min^{-1} (1), with 54 ml·(100 g)$^{-1}$·min^{-1} reported as an average figure for adult humans (22). CBF is higher in gray matter than in white matter; cortical blood flow is approximately 80 ml·(100 g)$^{-1}$·min^{-1}. CBF is higher in children (1,4), as is CMRO_2 (see the cerebral metabolism section above).

CBF Regulation

Present knowledge suggests that two basic mechanisms are involved in CBF control: myogenic control and chemical control (change in hydrogen ion concentration in the ECF of smooth muscle cells in the arteriolar walls).

Autoregulation. The ability of the vasculature in normal brain to alter its resistance so that CBF remains relatively constant over a wide range in CPP is termed autoregulation (Fig. 1). Discussion of proposed mechanism(s) of autoregulation is beyond the scope of this

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[3] It should be emphasized that the critical cerebral blood flow may vary with different anesthetics and may be different during isoflurane anesthesia than during enflurane or halothane anesthesia.

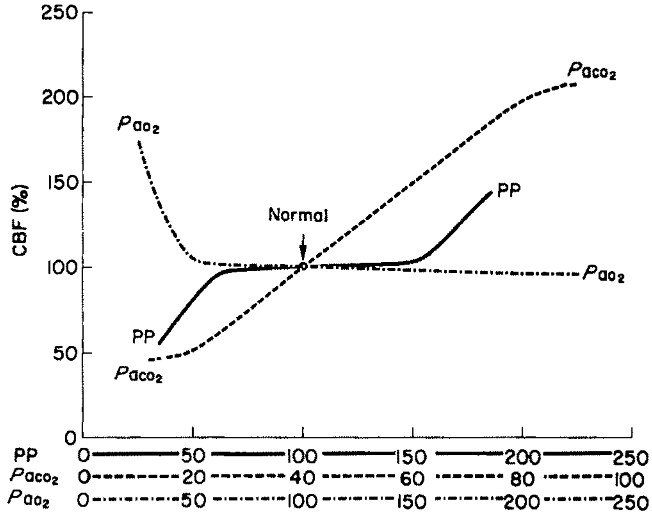

Figure 1. Relationship of cerebral blood flow (CBF) to perfusion pressure (PP), Paco$_2$, and Pao$_2$. (From Michenfelder JD. The cerebral circulation. In: Prys-Roberts C, ed. The circulation in anaesthesia: applied physiology and pharmacology. Oxford: Blackwell Scientific Publications, 1980:209–25. By permission.)

review. Of clinical importance, however, is the fact that cerebral arterioles (parenchymal vessels, as noted above) constrict when CPP increases and dilate when CPP decreases. The limits of autoregulation in normal humans are at a CPP of approximately 60 mm Hg at the lower end and 150–160 mm Hg at the upper end (20), although one author has suggested that the upper limit in normotensive humans occurs at an MAP of approximately 130 mm Hg (19). Beyond the limits of autoregulation, CBF becomes passively dependent upon CPP. When CPP increases above the upper limit of autoregulation, it exceeds the ability of the cerebral vasculature to constrict; CBF becomes directly related to, and passively dependent on, CPP, and the risks of cerebral edema or hemorrhage or both are increased.

The lower limit of CBF autoregulation is at a CPP below which maximal cerebral vasodilation has occurred and is inadequate to preserve flow, and CBF again becomes passively dependent on CPP (Fig. 1) (20). Note that this loss of autoregulation does not necessarily imply cerebral ischemia, but only that flow is directly related to CPP (see the critical cerebral blood flow section above). Based upon the idealized autoregulation curve, in patients with normal cerebral vessels, CPP theoretically can decrease by approximately 30% before the lower limit of autoregulation is reached (Fig. 1). This rule-of-thumb is useful clinically when planning the anesthetic management of a hypertensive, as well as a normotensive, patient.

In patients with chronic hypertension but without neurologic deficits, resting CBF is the same as in normotensive patients and is autoregulated. The autoregulatory curve is shifted to the right, however, placing both the upper and lower limits of autoregulation at higher perfusion pressures (23). A recent study in rats suggests that long-term antihypertensive therapy may reverse this shift (207). It is believed that the persistent high pressure produces adaptive changes in the form of arteriolar wall hypertrophy (19). In acute hypertension, this morphologic change has not occurred and the autoregulation curve is not shifted to the right. Note that increased sympathetic activity also temporarily shifts the autoregulatory curve to the right (1).

Autoregulation occurs only when cerebral vessels are intact and the brain is not damaged. It is abolished by hypercapnia, high concentrations of volatile anesthetics, hypoxia, trauma, and focal ischemia (1). Autoregulation usually is present during light levels of general anesthesia; this has been demonstrated with inhalation agents and is presumed to be true with intravenous agents such as barbiturates and narcotics.

Chemical regulation. ARTERIAL CO_2 PARTIAL PRESSURE (Paco$_2$). Normal cerebral vessels respond to changes in Paco$_2$ by dilating when Paco$_2$ increases and constricting when Paco$_2$ decreases. During normoxia, for the same CPP there is a fourfold change in CBF between Paco$_2$ 20 mm Hg and Paco$_2$ 80 mm Hg (Fig. 1). The primary mechanism involved in cerebrovascular response to change in Paco$_2$ or localized cerebral metabolic rate is believed to be a change in hydrogen ion concentration ($[H^+]$) in the ECF fluid of the smooth muscle cells in the arteriolar walls (20). Because CO_2 is unionized as a gas, and can readily diffuse into and out of the ECF, CO_2 is the most readily available clinical means of altering ECF $[H^+]$ and thereby affecting CVR. Other determinants of the ECF $[H^+]$ include CO_2 produced by local cerebral metabolism, CSF bicarbonate ion concentration ($[HCO_3^-]$), and lactic acid in pathologic states (20). In chronic hypercapnia or hypocapnia, CBF tends to return toward normal as adjustment in CSF $[HCO_3^-]$ returns ECF $[H^+]$ toward normal (20,24). Measurable adaptation to change in Paco$_2$ begins within 4–6 hr (20); complete adaptation requires 24–36 hr (20).

Although the direct effect of CO_2 on ECF $[H^+]$ in vascular smooth muscle is an important mechanism by which CO_2 affects CVR, it neither explains all reported observations concerning cerebrovascular CO_2 reactivity nor excludes other concomitant mechanisms. Observations in humans (1,25) and animals (1,25,26) indicate that neuronal reflexes influence the response of CBF to changes in Paco$_2$. In experimental preparations sympathetic stimulation decreases CBF during hypercapnia, whereas cervical sympathectomy enhances the response of CBF to hypercapnia; discrete brainstem lesions reduce the response of CBF to hypercapnia; and a decrease in cerebral metabolism lowers the cerebrovascular CO_2 reactivity, presumably through autonomic pathways (1,25,26). In anesthetized cats, the change in CBF for each one mm Hg change in Pa_{CO_2} varies in different parts of the brain (prosencephalon > cerebellum > brainstem> cervical cord > thoracic cord), correlating reasonably well with levels of tissue metabolism in these areas (25).

IONIC, NEUROGENIC ACTIONS. Changes in ion flux also influence CBF regulation. Among the findings of the perivascular microperfusion work of Betz and Csornai (27) are that increases in $[H^+]$ or $[K^+]$ cause pial arterial dilation while an increase in $[Ca^{2+}]$ causes pial arterial constriction.

ADENOSINE. Adenosine may contribute to the cerebral vasodilation associated with cerebral hypoxia (1). The enzyme that dephosphorylates adenosine monophosphate (AMP) to form adenosine is bound to the cell membrane (1). It is hypothesized that adenosine formed from AMP can cross the cell membrane and enter the ECF; an increased efflux of adenosine into ECF is associated with hypoxia (1). Once in the ECF, adenosine could act on resistance vessels to produce vasodilation. One problem with this hypothesis is that increased AMP would be required for increased formation of adenosine to occur, yet increased accumulation of AMP has not been found at hypoxic levels associated with maximal vasodilation (1).

"Luxury Perfusion"; Paradoxical Response to Pa_{CO_2}. As noted earlier, local accumulation of acid metabolites in areas with marginal perfusion causes cerebral vessels to dilate. Vasodilation of this type is termed vasomotor paralysis (8); the ability of the vessels to respond to changes in either perfusion pressure or Pa_{CO_2} is impaired or abolished, and flow is passively dependent on perfusion pressure. In this circumstance, normal or elevated perfusion pressure can produce flow that is "supernormal" relative to CMR_{O_2}, a phenomenon termed the "luxury perfusion syndrome" (8). If, in the absence of hypotension, CVR decreases in nonischemic regions of the brain (that is, in the "normal" cerebral vessels), blood may be shunted away from the area of vasomotor paralysis; such shunting has been termed the "intracerebral-steal syndrome" (8). If CVR increases in the normal vessels, blood may be shunted into the area of vasomotor paralysis, a phenomenon referred to as the "inverse-steal" or "Robin Hood" syndrome (8).

Vasomotor paralysis can occur within ischemic areas, around a tumor or area of infarction, or distal to vascular occlusions (8). Caution must be exercised in controlling MAP in patients in whom vasomotor paralysis may be present, because flow is passively dependent on perfusion pressure.

Clinically, CVR is affected in normal vessels primarily by altering Pa_{CO_2}. Although the potential for the paradoxical response to Pa_{CO_2} always must be considered in patients, it is important to remember that altering the Pa_{CO_2} does not produce either "steal" or "inverse-steal" in every patient with regional abnormalities of the cerebral circulation (8). Moreover, there is no practical clinical technique for measuring or predicting preoperatively in individual patients with vasomotor paralysis what will happen to CBF distribution when Pa_{CO_2} is changed. Recognizing the concomitant theoretical advantages and disadvantages of hypercapnia and hypocapnia in groups of patients with vasomotor paralysis, as well as our inability to predict CBF changes in an individual patient, we incorporate normocapnia in our anesthetic management of patients with ischemic cerebrovascular problems (for example, those undergoing carotid endarterectomy).

Rogers et al. (28) recently reported that chronic cigarette smoking apparently directly affects the cerebrovascular system, reducing flow to the gray matter before symptoms of cerebrovascular insufficiency become apparent. This effect may involve an affect on cerebral arteriosclerosis.

Anesthetic Effects on CMR_{O_2} and CBF

Autoregulation of CBF usually is present during light levels of general anesthesia but may be impaired or abolished by deep levels of anesthesia (see the CBF regulation section above). Cerebrovascular response to change in Pa_{CO_2} is retained and probably enhanced during anesthesia with inhalation agents; the slope of the CO_2 response curve is steeper, although the plateau levels are not altered significantly (Fig. 2) (20). At a mean end-tidal halothane concentration of 0.98%, CBF in humans varies linearly with Pa_{CO_2} between 20 and 50 mm Hg (Fig. 3). During anesthesia with intravenous agents, CO_2 responsivity is decreased. Anesthetic agents alter the metabolic rate of neurons only to the degree that they alter neuronal function (7). They have no significant effect on that portion of CMR_{O_2} related to maintenance of cellular integrity. The relative effects of anesthetic agents on CMR_{O_2} and CBF are summarized in Table 1.

Intravenous Agents

Barbiturates. Barbiturates affect the cerebral metabolism only of functioning neurons, in which they de-

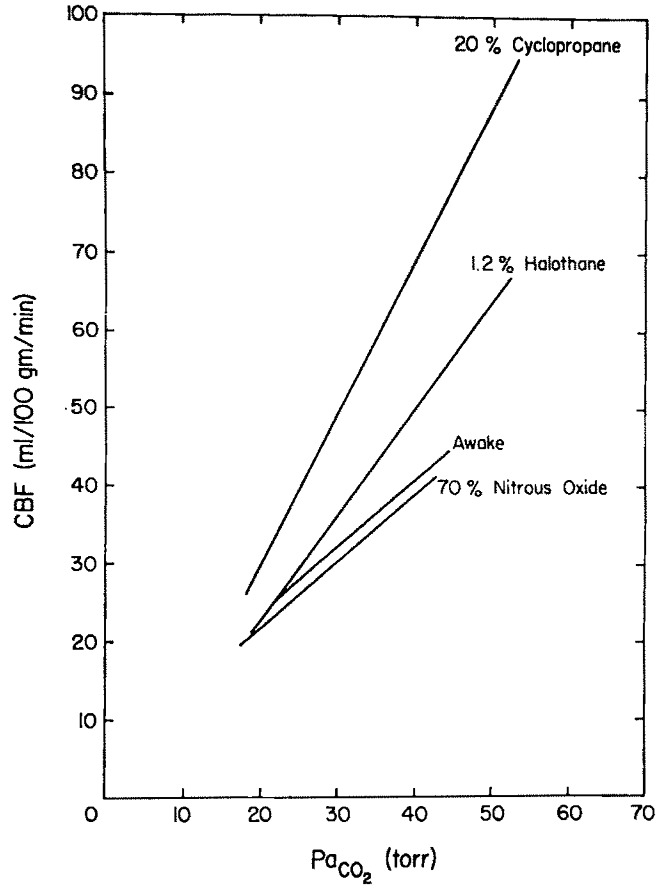

Figure 2. The sensitivity of CBF to $PaCO_2$ "awake" and anesthetized. The "awake" line was adapted from the data of Kety and Schmidt (22). Modification was necessary because those workers reported higher normocapnic CBF and $CMRO_2$ values with the older form of the N_2O-uptake technique for CBF determination than those presently obtained using ^{86}Kr and venous extrapolation. Their CBF values, therefore, were multiplied by the factor: $CMRO_2$ with extrapolation technique/$CMRO_2$ with original technique = 0.658, so that comparison on the same basis would be possible. "Awake" data obtained with the modified technique are not available. (From Smith AL, Wollman H. Cerebral blood flow and metabolism: effects of anesthetic techniques. Anesthesiology 1972;36:378–400. By permission of JB Lippincott Company.)

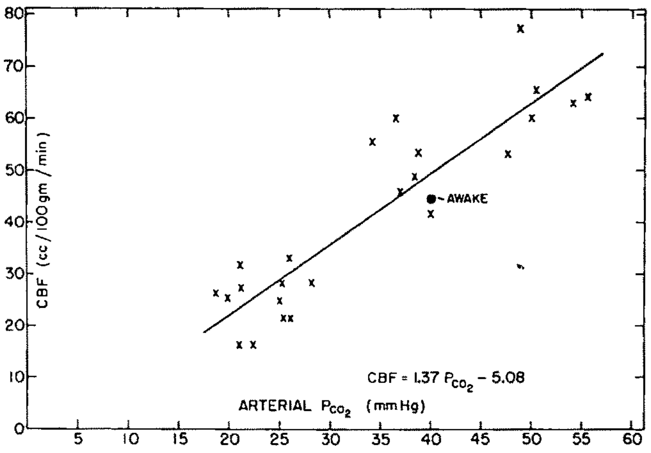

Figure 3. Cerebral blood flow as a function of $PaCO_2$ during halothane anesthesia in normal man. The awake point represents the mean value measured by the same method in normal conscious man (44.4 ml·(100 g)$^{-1}$·min^{-1}). (From Alexander SC, Wollman H, Cohen PJ, Chase PE, Behar M. Cerebrovascular response to $PaCO_2$ during halothane anesthesia in man. J Appl Physiol 1964;19:561–5. By permission of the American Physiological Society).

press cerebral activity and reduce $CMRO_2$ in a dose-dependent manner (1,29). If $PaCO_2$ is maintained constant, CBF decreases in parallel with $CMRO_2$ (1,30). The presumed mechanism is a decrease in neuronal function leading to a decrease in O_2 demand resulting in an appropriate decrease in CBF. At levels of anesthesia that are adequate for surgery, $CMRO_2$ in humans decreases 36–45%. Slowing and burst suppression appear on the EEG at approximately 60% of normal $CMRO_2$. In dogs, Michenfelder demonstrated that an infusion rate of thiopental of 2 mg·kg^{-1}·min^{-1} produced an isoelectric EEG at a $CMRO_2$ that was 46% of control and that continuing the infusion (with cardiovascular support by extracorporeal circulation) resulted in no further decrease in $CMRO_2$ (31). Studies using other barbiturates show a similar dose-dependent depression of $CMRO_2$, presumably secondary to barbiturate-induced depression of neuronal activity. It has been postulated that barbiturates decrease membrane excitability and impulse traffic and thereby decrease the demand for ATP production (29).

Benzodiazepines. CNS effects of benzodiazepines include serotonin antagonism, release of γ-aminobutyric acid (GABA) and facilitation of its neuronal activity, and decreased release or turnover (or both) of acetylcholine (32). Most reports indicate that benzodiazepines decrease CBF and $CMRO_2$. Comparison of different studies is complicated by differences in drug dosages, patient populations, and study protocols.

DIAZEPAM. In comatose patients with diffuse brain damage due to head trauma, in whom $CMRO_2$ was low, the intravenous administration of 50 mg of diazepam decreased $CMRO_2$ an additional 25% (33).

In eight patients without permanent neurologic symptoms and with normal carotid arteriograms and normal awake CBF values, the intravenous administration of 10 mg of diazepam plus 10 μg of fentanyl per kg, in the presence of 60% nitrous oxide, reduced CBF by 34% and $CMRO_2$ by 34.5% (34).

Compared with control anesthetic conditions (60–70% nitrous oxide and <0.1% inspired halothane) the intravenous administration of 0.3 mg of diazepam

Table 1. Relative Effects[a] of Anesthetic Drugs on CBF and CMRo$_2$

Drug	CBF	CMRo$_2$	CBF/CMRo$_2$
Halothane	↑ ↑	↓	↑
Enflurane	↑	↓ ↓	↑
Isoflurane	↑	↓	↑
Methoxyflurane	↑	↓	↑
Cyclopropane	↓ ↑	↓ ↑	↑
Ether	↓ ↑	↓ ↑	↑
N_2O	? ↑	? ↓	? ↑
Barbiturates	↓ ↓	↓ ↓	—
Narcotics	↓	↓	—
Droperidol	↓	?-	↓
Ketamine	↑ ↑ ↑	?-	↑
Althesin	↓ ↓	↓ ↓	—

[a]Key: ↑ ↑ ↑, greatly increased; ↑ ↑, moderately increased; ↑, mildly increased; ? ↑, possibly increased (data not firm); —, no change; ↓ ↑, biphasic effect, with initial decrease followed by increase; ↓, mildly decreased; ↓ ↓, moderately decreased.

From Michenfelder JD. The cerebral circulation. In: Prys-Roberts C, ed. The circulation in anaesthesia: applied physiology and pharmacology. Oxford: Blackwell Scientific Publications, 1980:209–225. By permission.

per kg produced no significant decrease in canine CMRo$_2$ but decreased CBF by 45–50% ($P < 0.05$) (35). It should be noted that the control CBF in this study was high (119 ml·min^{-1}·(100 g)$^{-1}$). Diazepam, 3 mg/kg, decreased CMRo$_2$ by approximately 20% and CBF by approximately 55–60%, whereas 7.5 mg/kg decreased CMRo$_2$ approximately 28% from control but did not produce significantly different changes in CBF or MAP compared to the 3 mg/kg dose (35). Substitution of nitrogen for N_2O did not produce significant differences in CMRo$_2$ or CBF.

MIDAZOLAM. In eight healthy adult volunteers, the intravenous administration of 0.15 mg of midazolam per kg decreased CBF by 33% (39% when corrected for a Pa_{CO_2} of 40 mm Hg) (36). All subjects slept after the midazolam injection was given, and all had antegrade amnesia lasting approximately 25 min (36).

In dogs anesthetized with 60–70% N_2O and <0.1% halothane, 0.2 mg/kg of midazolam produced no significant change in CMRo$_2$ but decreased CBF approximately 45% from control (60–70% N_2O, <0.1% halothane) (35). MAP decreased approximately 29%. Subsequent increasing doses (2.0, 5.0, and 10.0 mg/kg of midazolam) resulted in 24%, 34%, and 40–45% decreases in CMRo$_2$, respectively, accompanied by 64–70% decreases in CBF. MAP decreased approximately 40% with a 2 mg/kg dose and did not decrease beyond this point with subsequent doses (35). The significant decrease in CBF after the initial doses of diazepam and midazolam may be explained on the basis of the elevated control CBF values, presumably due to the use of N_2O. In the absence of N_2O in the same canine model, a similar dose of diazepam produced declines of approximately 15% in both CBF and CMRo$_2$ (37).

LORAZEPAM. In conditioned monkeys, lorazepam, 4 mg/kg (a very high dose compared to clinical use in humans) administered intravenously, decreased CBF by 26%, CMRo$_2$ by 21–30%, and CMR$_{glucose}$ by 42% (38). Lorazepam reduced CBF and metabolism in every monkey. It is interesting that such uniformity of response has not been reported with diazepam, perhaps because of differences in species, dose levels, or experimental conditions (39). Reportedly, lorazepam is more potent and better absorbed after intramuscular injection than diazepam and has a more prolonged duration of action than does diazepam after intravenous administration.

Although in some animal species benzodiazepines tend to reduce CBF more than CMRo$_2$, we are not aware of any evidence that this occurs in humans. Benzodiazepines in appropriate doses can be used as anxiolytic agents in patients with neurologic problems, and have been used to treat seizures. Once absorbed, benzodiazepines can produce greater effects on the central nervous system in the elderly (defined as 65 years old or older by Thompson et al. (38)) because of increased sensitivity of target organs and impaired drug disposition (38).[4] In the elderly or in patients with hepatic or renal impairment, short-acting benzodiazepines are preferable to long-acting ones and the recommended dosage is 30–50% of that for younger patients (38).

Because of the relationship between CBF and Pa_{CO_2}, it is important to evaluate the respiratory effects of pharmacologic agents that may be used in patients with CNS pathology. In seven healthy volunteers, neither 0.15 mg of diazepam nor 0.075 mg of midazolam per kg (30-sec intravenous infusion) produced statistically significant respiratory depression (40). Minimal values of the slope of the CO_2 response curve occurred 15 min after diazepam injection and 3 min after midazolam injection.

Narcotics. The effects of narcotics on CMRo$_2$ and CBF, particularly in humans, are not well defined (20,41). Results vary in different studies. In general, in the absence of significant changes in Pa_{CO_2} or temperature, premedicant doses of narcotics do not significantly alter $CMRo_2$ or CBF. In large doses (for example, morphine ≥1 mg/kg), morphine and meperidine depress $CMRo_2$ slightly (1).

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[4] Drug disposition in the elderly often is changed significantly due to decreased lean body mass and total body water, increased total body fat, and decreased serum albumin (38). Elimination half-life frequently is increased owing to increased volume of distribution or decreased clearance (38).

MORPHINE. In normocapnic, normothermic dogs receiving <0.1% halothane with a 70:30 mixture of N_2O and O_2, incremental doses of 0.2 mg/kg of morphine decreased $CMRo_2$ by 15% at a total morphine dose of 1.2 mg/kg, with no further decrease in $CMRo_2$ at doses of 2.0 and 3.0 mg/kg (42). CBF decreased to 30% and 50% of control at doses of 0.2 and 0.6 mg/kg, respectively (42). Cerebral metabolic pathways appeared to be unaltered, with no change in the oxygen–glucose index (OGI) (42).

Using a hydrogen clearance technique, Matsumiya et al. (43) reported that the intravenous administration of morphine (1 mg/kg) produced statistically significant decreases in canine CBF, $CMRo_2$, and $CMR_{glucose}$. Thirty minutes after morphine administration, CBF was 78 ± 13% of control, $CMRo_2$ 70 ± 17%, and $CMR_{glucose}$ 56 ± 18%. At 60 min, CBF was 73 ± 14% of control, $CMRo_2$ 74 ± 25%, and $CMR_{glucose}$ 50 ± 12%. Naloxone (40 μg/kg) administered intravenously 60 min after the morphine returned CBF, $CMRo_2$, and $CMR_{glucose}$ to control levels (43). In a separate experiment this dose of naloxone alone did not produce any significant change in CBF, $CMRo_2$, or $CMR_{glucose}$, but did block the effect of subsequent intravenous administration of 1 mg/kg morphine on CBF and $CMR_{glucose}$ (43). The subarachnoid administration of 0.2 mg/kg of morphine produced no significant changes in CBF, $CMRo_2$, or $CMR_{glucose}$ (43).

MEPERIDINE. Meperidine (2 mg/kg) administered intravenously to normocapnic dogs anesthetized with halothane (0.8–0.9% end-expired) and O_2 produced a decrease of 13% in $CMRo_2$ with no significant change in CBF (44).

FENTANYL. In normocapnic, artificially ventilated rats, intravenously administered fentanyl in doses of 25, 50, 100, 200, or 400 μg/kg produced dose-related decreases in both $CMRo_2$ and CBF (41). Maximal depression occurred at 100 μg/kg, at which $CMRo_2$ and CBF were depressed by 35% and 50%, respectively (41). Previous work involving smaller doses of fentanyl (generally 5 μg/kg or less) suggested no significant change in $CMRo_2$ (1,41). In dogs initially anesthetized with pentobarbital (30 mg/kg intravenously), fentanyl (25 μg/kg intravenously) did not produce a significant change in CBF or $CMRo_2$, did not alter the cerebrovascular responses to hypoxia or hypercapnia, and did not alter the upper or lower limits of cerebral autoregulation (45). To study autoregulation, blood pressure was lowered by hemorrhagic hypotension and increased slowly by intravenous infusion of norepinephrine (45). During hypoxia, CBF increased sufficiently to maintain O_2 delivery. (45).

Droperidol. The effects of neuroleptic agents on CBF and $CMRo_2$ have not been defined in humans (20). Clinical evidence suggests that they decrease CBF, with little change in $CMRo_2$ (20).

Etomidate. Etomidate decreases CBF and $CMRo_2$ in humans (46). This is accompanied by pronounced suppression of cortical electrical activity noted on the EEG (47). As with the other anesthetics, the presumed mechanism of action is depression of cerebral metabolic rate secondary to the decrease in cortical electrical activity. In seven patients, etomidate (intravenous 15-mg bolus for 1 min, followed by infusion at 2–3 mg/min) produced statistically significant decreases of 36% in CBF and 45% in $CMRo_2$, with no significant change in MAP, $Paco_2$, Pao_2, or arterial–venous O_2 content difference ($C(a-v)o_2$) (46). In anesthetized (propranolol, N_2O, O_2, 0.1–0.4% halothane), ventilated patients, etomidate (0.2 mg/kg) produced a significant reduction of 32–34% in CBF 30 sec after injection but no significant change in CBF at 5 and 10 min after the injection (48). By comparison, methohexitone (1 mg/kg) significantly reduced CBF by 43–45% at 30 sec and 22% at 5 min but produced no significant change at 10 min; whereas thiopental (4 mg/kg) significantly reduced CBF by 44% at 30 sec, 44% at 5 min and 45% at 10 min. Wagner et al. (49) recently reported that the use of etomidate can be followed by inhibition of adrenal steroidogenesis; the clinical implications are not clear at this time.

Ketamine. Significant abrupt increases in CBF produced by ketamine do not depend upon increased MAP (20). In humans, ketamine has no significant effect on $CMRo_2$, but in dogs, an increase in $CMRo_2$ of 10% accompanies ketamine-induced increases in CBF (20). Intravenous ketamine (10 or 30 mg/kg) reduced the local cerebral glucose utilization in some portions of the rat brain while increasing it in others (50). Local central glucose utilization decreased in the auditory and sensory-motor areas, but increased in the limbic system (largest increases), in the extrapyramidal motor system, and in the corpus callosum (50). These results are consistent with previous reports of ketamine-induced limbic seizure activity and with the auditory and somatosensory deprivation superimposed on an active but metabolically disorganized CNS, which are characteristic of ketamine "anesthesia." Ketamine directly dilates constricted segments of isolated strips from canine middle cerebral, basilar, and mesenteric arteries, apparently by mechanisms that do not involve adenosine, prostaglandins, cholinergic receptors, or β-adrenergic receptors (51).

Inhalation Agents

N_2O. Because N_2O is widely used in clinical practice, and frequently in both the control and drug-study periods in experimental work, there is great interest in its effects on $CMRo_2$ and CBF. Unfortunately, considerable discrepancy exists in published reports, chiefly because of differences in experimental design (1). Results in humans suggest that 70% N_2O depresses $CMRo_2$ by 2–23%, depending on the conditions of the study (1). In normothermic, artificially ventilated, paralyzed, sympathectomized, vagotomized dogs, $CMRo_2$ increased 11% with 70% N_2O over that with 70% N_2 (52). With halothane concentrations of 0.4 and 0.7%, $CMRo_2$ was greater with 70% N_2O than with 70% N_2, but the difference was not statistically significant. N_2O, 60% administered to halothane-anesthetized dogs (53) and 70% to unmedicated goats (54), reportedly more than doubles $CMRo_2$ and CBF. Studies in β-blocked or adrenalectomized rats showed $CMRo_2$ and CBF to be similar with 70% N_2O or 70% N_2 (1). Clinical results suggest that 70% N_2O has minimal effect, or no effect at all, on $CMRo_2$ and CBF (1).

Volatile Agents

Halothane, Enflurane, and Isoflurane. Like the barbiturates, halothane, enflurane, and isoflurane qualitatively decrease $CMRo_2$; unlike the barbiturates, they tend to increase CBF (20). The increase in the ratio of CBF to $CMRo_2$ ($CBF/CMRo_2$) is related to concentration and is approximately linear (assuming CPP is maintained within the autoregulatory range) (20). The explanation for this "uncoupling" of the $CMRo_2$–CBF relationship has not been clarified. Michenfelder noted that the uncoupling may represent a "resetting" of the $CMRo_2$–CBF relationship because of higher tissue Po_2 demand (20). At equivalent minimum alveolar concentration (MAC) levels, halothane is a more potent cerebral vasodilator than enflurane or isoflurane in humans (20–25% CBF increase at 1 MAC), (1,20) and animals (55), whereas enflurane and isoflurane are more potent depressants of $CMRo_2$ (8,20,55). In cats anesthetized with 75% N_2O–25% O_2, the addition of 1 MAC enflurane or isoflurane reduced $CMRo_2$ to approximately 50% of control (55). The decrease in canine $CMRo_2$ with increasing MAC is nonlinear for halothane, enflurane, and isoflurane (30). The point at which the decline in the rate of $CMRo_2$ slows coincides with the change in EEG voltage dominance from posterior to anterior cerebral hemisphere and approximates 0.4 MAC.

At deeper levels of anesthesia with halothane, enflurane, or isoflurane, the autoregulation of CBF is lost and flow becomes passively dependent upon perfusion pressure (20). Cerebrovascular responsiveness to changes in $Paco_2$ is retained, however (19,56). Retention of CO_2 reactivity is of importance in patients in whom a potential increase in ICP due to increase in intracranial blood volume can be prevented by inducing hypocapnia before administering a volatile agent that is a cerebral vasodilator.

That halothane in anesthetic concentrations depresses $CMRo_2$ and is a cerebral vasodilator is established (1). The degree to which $CMRo_2$ is depressed varies considerably in different studies, however, owing at least in part to differences in experimental technique (for example, methods of measurement, type of anesthetic, induction, use of adjuvant agents) and species. In humans, 1% halothane reduced $CMRo_2$ by approximately 25% (20). In dogs, 0.5% halothane in 70% N_2O reduced $CMRo_2$ by approximately 17% (57). High concentrations of halothane administered to dogs (with hemodynamic support by extracorporeal circulation) affected $CMRo_2$ differently than did high doses of thiopental (58). Whereas continued infusion of thiopental beyond the isoelectric EEG point did not depress $CMRo_2$ below a "basal" 2.2 ml $O_2 \cdot (100\ g)^{-1} \cdot min^{-1}$ and did not produce abnormal levels of cerebral metabolites, concentrations of halothane above 2.3% produced a dose-related decrease in $CMRo_2$ accompanied by a dose-related reversible alteration in oxidative phosphorylation (58). Thus high concentrations of halothane potentially are detrimental (58).

In the absence of electrographic seizures, 2–3.2% enflurane in man produced a decrease of 33–50% in $CMRo_2$ (1,59). No significant change in hemispheric CBF occurred during anesthesia with 2% enflurane–67:33 N_2O and O_2 mixture–pancuronium anesthesia (control: 67:33, N_2O:O_2–pancuronium) after angiography in adult patients without overt increased ICP (60). Systolic and mean arterial blood pressures decreased significantly (28 and 27 mm Hg, respectively), but diastolic pressure and cardiac output did not. In normocapnic patients in whom CPP was maintained above 60 mm Hg (phenylephrine infusion as required), 2% enflurane produced no significant change in CBF, $CMRo_2$, $CMR_{glucose}$, or OGI (61). Enflurane (3.5%) produced a significant increase in CBF and a significant (17%) decrease in $CMRO_2$, with no significant change in $CMR_{glucose}$ or OGI (61). At 3.5% enflurane, the EEG showed frequent spikes and suppression. Sakabe et al. (61) concluded that enflurane is a cerebral vasodilator, increasing the CBF and decreasing the $CMRO_2$ at an anesthetic level that is characterized on the EEG by suppression and frequent spikes.

In normocapnic, normothermic dogs, 2.2% enflurane decreased hemispheric $CMRO_2$ by 34% with no significant changes in CBF, $CMR_{glucose}$, or OGI (59). There were no statistically significant changes in CSF pressure or CVR, although CVR tended to decrease. MAP decreased 34% (59). At an end-expired enflurane concentration of 2.2%, the CBF response to changes in $PaCO_2$ was comparable to that for other halogenated anesthetic agents and was accounted for entirely by changes in CVR (59). As noted earlier, the $CMRO_2$ dose–response curve is nonlinear at concentrations of enflurane less than 1 MAC (canine MAC is 2.2% enflurane). The EEG shifted from an "awake" to an "anesthetized" pattern between approximately 0.3 and 0.4 MAC, at which time CBF was ≥90% of control and $CMRO_2$ was 80–85% of control (30). At 0.5 to 0.6 MAC, with an "anesthetized" pattern on the EEG, CBF and $CMRO_2$ were approximately 85% and 72–75% of control, respectively (30).

Seizure activity during enflurane anesthesia presumably is minimized by avoiding hypocapnia and enflurane concentrations >1.5 MAC (59). Enflurane depresses tonic neuronal activity of the midbrain reticular formation, which may explain its epileptogenic effect (62). In 10 hypocapnic patients with normal hearing, statistically significant delays in brainstem auditory evoked response (BAER) latency occurred at 2–3% enflurane (62).

Among the volatile agents, isoflurane possesses some unique properties. Only isoflurane produces an isoelectric EEG pattern when administered in a clinical concentration (isoelectricity at 2 MAC: 2.4% in humans) that is tolerated hemodynamically (63). The cerebral metabolic effects of this concentration are similar to those of thiopental administered in doses sufficient to abolish EEG activity. Isoflurane produces dose-related decreases in $CMRO_2$. Once EEG isoelectricity (that is, "basal" $CMRO_2$) is reached, however, further increases in isoflurane do not produce further decreases in $CMRO_2$ (63). At isoflurane-induced EEG isoelectricity, the cerebral metabolic energy profile remains normal (63). Unlike halothane, isoflurane in high concentrations appears to have no toxic effect on oxidative phosphorylation (63).

At 1 MAC, isoflurane does not significantly increase CBF in man (64,65) but does (to between approximately 120 and 133% of control) in dogs (64) and cats (55). In normocapnic, normotensive volunteers, no significant CBF change occurred at 0.6–1.1 MAC, but CBF doubled at 1.6 MAC isoflurane (65). This compares with a tripling of CBF at 1.6 MAC halothane (65). Because both isoflurane and halothane decrease $CMRO_2$, the smaller increase in CBF with isoflurane than with halothane at a given MAC may be due to a smaller increase in vascular cyclic-AMP relative to ATP (65). No evidence of epileptogenic EEG activity or overt convulsive activity has been noted with isoflurane, even with increasing depth or hypocapnia or both (64).

Other Agents

Catecholamines, Angiotensin, Adrenergic Antagonists. The blood brain barrier (BBB) separating the blood from the brain and CSF is located at the choroid plexus, brain and subarachnoid vessels, and arachnoid membrane. It is composed of cells (vascular endothelial, choroid plexus epithelial, arachnoid, and perineural) connected by tight junctions that restrict intercellular diffusion and thereby force solute exchange to occur through the cells. It regulates the composition of the microenvironment of neurons, axons, and glia (66).

Normally, the tight intercellular junctions plus the presence of DOPA decarboxylase and monoamine oxidase in the endothelial cells of the cerebral pericytes and capillary walls in the intact BBB prevent the passage from blood to brain of small-to-moderate amounts of epinephrine, norepinephrine, dopamine, or serotonin (67). Under these circumstances, circulating catecholamines do not significantly affect $CMRO_2$. If BBB permeability is increased (for example, by hypertension or osmotic disruption), epinephrine and norepinephrine can enter the brain (67–69) where they reversibly increase $CMRO_2$ (67). In unanesthetized patients requiring regional CBF study and angiography, the injection into the internal carotid artery of epinephrine (2–10 μg/min for 4–12 min), norepinephrine (0.2–20 μg/min for 4 to 12 min), or angiotensin (0.25–2 μg/min for 4–12 min) caused no significant change in regional or hemispheric mean CBF. The increase in MAP secondary to the intravenous injection of norepinephrine and angiotensin increased CBF in severely ill patients with cerebral tumors or apoplexy (70), presumably because of the loss of autoregulation and the presence of vasomotor paralysis.

Most of the evidence suggests that systemically administered α- and β-receptor agonists and antagonists do not significantly alter CBF (or $CMRO_2$) unless their hemodynamic effects result in a CPP that exceeds the limits of autoregulation (20). As noted earlier, the BBB probably is a significant element in the lack of effect of catecholamines on CBF and $CMRo_2$ (20).

Experimental studies are suggestive—but not declarative—of a neurotransmitter function for angiotensin or an angiotensin-like peptide (71). In other experiments, angiotensin produced constriction of pial precapillary vessels and contraction of isolated segments of the feline middle cerebral artery (72).

Prostaglandins, Indomethacin. Cerebral blood vessels can synthesize prostaglandins, including prostacyclin (PGI_2) and all primary prostaglandins (74). The substrate for both thromboxane-A_2 and PGI_2 is the cyclic endoperoxide PGH_2 (74). Prostacyclin synthetase, the enzyme that converts PGH_2 to PGI_2, is located in the endothelium of blood vessels (75). Thromboxane synthetase, the enzyme that converts PGH_2 to thromboxane-A_2, is found in platelets (74). PGI_2 is a vasodilator and potent inhibitor of platelet aggregation, whereas thromboxane-A_2 is the most potent cerebral vasoconstrictor known and stimulates platelet aggregation (73,74). At the normal blood–endothelial interface there may be a reciprocal relationship between intramurally generated PGI_2 and extramurally generated thromboxane-A_2 (73,74). In addition to their roles in normal CBF control, prostaglandins and allied compounds appear to be involved in some cerebral pathologic states (73). Thromboxane-A_2 may be a prime factor in cerebral vasospasm (73). Prostaglandins may be involved in the cerebral ischemia that follows head injury (73).

Indomethacin is a cyclooxygenase inhibitor. When administered in doses of 1.5 or 4 mg/kg to dogs before ischemia produced by CSF compression, indomethacin enhanced postischemia reperfusion (74). The administration of indomethacin after the induced ischemia did not produce flows different from those in untreated dogs (74). In anesthetized Wistar rats, indomethacin (10 mg/kg intravenously) decreased CBF but did not alter $CMRo_2$ (75). It curtailed the cerebral vasodilation produced by hypercapnia ($Paco_2$ approximately 80 mm Hg) but not that due to hypoxia (Pao_2 approximately 25 mm Hg). Thus indomethacin influenced normal cerebrovascular tone and altered CBF-$CMRo_2$ coupling.

Muscle Relaxants

An ideal muscle relaxant should have rapid onset of action, no significant cardiovascular effects, no significant cumulative effects, minimal dependence on hepatic or renal elimination, a short duration of action, a wide margin between relaxant doses and doses that inhibit autonomic nervous sytem activity, and easy and dependable reversal of the muscle paralysis (76,77). For endotracheal intubation of the patient with intracranial pathology, a relaxant with rapid onset and no significant cardiovascular effects is particularly important. In the patient with vasomotor paralysis and potential or overt intracranial hypertension due to a space-occupying mass, goals include the maintenance of CPP while simultaneously avoiding an increase in intracranial blood volume, and the rapid production of profound muscle paralysis to avoid an increase in intracranial venous pressure and hence ICP (see the intracranial pressure section below). In a patient with the potential for neuronal ischemia due to cerebrovascular disease, the hemodynamic goal is to support or improve CPP by maintaining or moderately increasing MAP, again avoiding hypertension and its attendant intracranial risks in the patient with vasomotor paralysis.

The ideal agent remains a goal. Because cumulative effects, duration of action, mode of elimination, and ease of antagonism are more related to systemic considerations than neurologic factors per se, we will focus on hemodynamic effects, rapidity of onset, and relative disadvantages and contraindications to different relaxants in patients with neurologic problems.

Succinylcholine. Succinylcholine frequently is chosen when rapid onset and short duration of neuromuscular blockade are desired. Contraindications to the use of succinylcholine in patients with thermal trauma, direct muscle trauma, or neurologic motor deficits have been reviewed (78). Reported increases in ICP after laryngoscopy and intubation facilitated by succinylcholine, and in animal studies of intracranial hypertension, have led some physicians to regard increased ICP as a relative contraindication to succinylcholine use (79,80–82). Proposed mechanisms for an increase in ICP after succinylcholine use include increased CVP (and hence increased cerebral venous pressure) due to muscle fasciculations; increased MAP, leading to increased intracranial blood volume if autoregulation is not functioning; and interference with jugular venous drainage during laryngoscopy (which could occur without regard to the specific neuromuscular blocking agent) (79). Recent reports of the use of succinylcholine in patients with intracranial tumors (82) or nonacute subarachnoid hemorrhage (83) and in dogs with experimentally induced intracranial mass lesions (84,85) suggest that succinylcholine can be used to facilitate intubation in neurologic patients who are adequately anesthetized and whose blood pressure and $Paco_2$ are controlled (79,83). Muscle fasciculations may be minimized by pretreatment with a nondepolarizing relaxant (79). We use succinylcholine, in conjunction with appro-

Table 2. Hemodynamic Effects of Nondepolarizing Muscle Relaxants

			Mechanism			
Drug	Blood pressure	Heart rate	Histamine release	Vagolytic effect	Indirect sympathomimetic effect	Ganglionic blockade
Pancuronium	—	↑ (mild)	—	1[a]	2[a]	
Metocurine[b]	Little or no change		Weak, if injected rapidly (5–10 sec). None if injected slowly (30–60 sec)			
Atracurium[b]	Transient ↓ BP possible with rapid injection (5–10 sec) of large dose		As above			
Vecuronium[b]	None	None	—	Very weak; not within clinical dose range		
d-Tubocurarine	↓	—	1[a]			2[a]
Gallamine	—	↑ (moderate)	—	1[a]	2[a]	

[a] Numbers refer to relative importance of mechanisms.

[b] The lack of cardiovascular effect of these drugs frequently results in some bradycardia during general anesthesia, especially with fentanyl, morphine, or halothane. This may require treatment with an anticholinergic.

Modified with permission from Savarese JJ: Clinical use of muscle relaxants. In: 1984 Review course lectures. Cleveland: International Anesthesia Research Society, p. 148.

priate control of blood pressure and $Pa\text{CO}_2$, to facilitate intubation in patients in whom rapid control of the airway or rapid onset and dissipation of the neuromuscular block (or both) are indicated.

Undesirable hemodynamic changes may accompany the use of succinylcholine. Transient decreases and increases in MAP have been reported (81). Searching for an explanation for the hypertension that is sometimes noted, Nigrovic et al. (86) reported that 1 mg/kg of succinylcholine administered as an intravenous bolus to hemodynamically stable, ventilated, and anesthetized (N_2O–O_2–halothane) patients (ASA status I or II) produced an increase of approximately 60% in plasma norepinephrine ($P < 0.01$) with no change in plasma epinephrine or dopamine levels. The patients had not been intubated or subjected to surgery at the sampling times. Blood pressure did not change significantly. Plasma norepinephrine levels increased immediately after the injection of succinylcholine, peaked at approximately 3 min, and returned to preinjection levels by 10 min. Metocurine (0.3 mg/kg) did not produce a significant change in plasma catecholamine levels in a comparable group of patients.

Nondepolarizing relaxants. The pharmacology, neuromuscular effects, and hemodynamic effects of nondepolarizing muscle relaxants have been reviewed in multiple articles (76,77,87–90), texts, and monographs. The importance of controlling MAP in patients with intracranial pathology has been discussed earlier in this article. Both atracurium and vecuronium appear to have clinically insignificant cardiovascular effects compared with pancuronium (76,77,87–89), and their use may prove to be advantageous in patients with intracranial disease. The relative hemodynamic effects of the nondepolarizing relaxants are summarized in Table 2 (90).

Atracurium is inactivated rapidly by Hofmann elimination at physiologic temperature and pH (91). The main metabolite is laudanosine (91). In quantities related to therapeutic doses of atracurium, neither laudanosine nor other breakdown products of atracurium should have significant neuromuscular or cardiovascular effects (91). Large doses of laudanosine have been reported to produce seizures in dogs (208). In dogs anesthetized with tetracaine spinal anesthesia plus an expired halothane concentration just sufficient to produce an EEG sleep pattern (0.55–0.75%), 1.0–2.5 mg/kg of atracurium produced EEG evidence of arousal, which did not return to control levels in six of six dogs (209). CMR, CBF, and ICP for the group did not change significantly during arousal. This EEG arousal after atracurium use was abolished by anesthetic (1 MAC) concentrations of halothane and is presumed to be due to laudanosine (209).

Histamine

The usual histamine levels in human plasma approximate 1 ng/ml, with a probable plasma half-life of less than 2 min (92). Histamine release can accompany the use of some narcotics and muscle relaxants. Histamine can produce tachycardia (perhaps partly from catecholamine release), hypotension, peripheral vasodilation, increased vascular permeability, positive cardiac inotropic effect (via H_2 receptors), increased coronary blood flow, and significant changes in the ventricular fibrillation threshold (animal experiments; isolated perfused human heart) (92,93). Hypotension and tachycardia are the clinical signs most commonly noted with histamine release (92), with tachycardia occurring at mean plasma histamine levels lower than those associated with flush or hypotension (92). The effect of histamine on CBF in an individual patient will depend upon the relative changes in CVR and MAP produced by the histamine, whereas increased vascular permeability could result in cerebral edema. Morphine can produce significant release of histamine; recent reports suggest that fentanyl, sufentanil, butorphanol, and methadone do not (92).

In clinical studies, 0.25–0.75 mg/kg of *d*-tubocurarine administered as an intravenous bolus produced significance changes in pulse rate, blood pressure, and plasma histamine levels in patients anesthetized with fentanyl (3 μg/kg), thiopental (6 mg/kg), and $N_2O–O_2$ (92). Although there was significant variability in the peak plasma histamine level after a given dose of *d*-tubocurarine, there was an increased probability of histamine release as the *d*-tubocurarine dose was increased (92). In contrast, the bolus administration of 0.25 mg/kg of metocurine appears not to produce histamine release or hemodynamic changes (92).

Atracurium can produce histamine release, but its histamine-releasing property relative to its neuromuscular blocking potency approximates only one-third that of tubocurarine and one-half that of dimethyltubocurarine (93). Other studies suggest that plasma histamine levels do not change significantly when atracurium is administered in twice the ED$_{95}$ dose for neuromuscular block (93).

The cardiovascular responses mediated by histamine release have been reported to be attenuated by appropriate prophylactic use of H_1 and H_2 antagonists (92), for example, diphenhydramine and cimetidine.

Spinal Cord

The principles of neuronal protection apply to the spinal cord as well as the brain.

Spinal Cord Blood Flow

In anesthetized dogs (chloralose, urethane (94), halothane (43)) and sheep and lambs (chloralose, urethane (94)), spinal cord blood flow approximates 40% of CBF, as measured by hydrogen clearance (43) and 15-μm labeled microsphere (94) techniques. Flow to the thoracic cords is approximately 40% less than flow to either the cervical or the lumbosacral portions of the cord, perhaps because of a lower gray:white matter ratio in the thoracic cord (94). In the lumbosacral cord in sheep, gray matter flow is approximately fourfold greater than white matter flow (94).

As with the cerebral circulation, spinal cord blood flow (94) exhibits autoregulation and chemical regulation. During normoxia and normocapnia, autoregulation maintains total and regional spinal cord blood flow (94,95). In anesthetized dogs (70% N_2O, 0.5% halothane; or 70% N_2O plus 25 mg/kg of pentobarbital), thoracic spinal cord blood flow (^{133}Xe clearance) did not change significantly when arterial pressure was varied from 60 to 150 mm Hg (graded hypotension produced by bleeding the dogs) (95). Below arterial pressures of 60 mm Hg, spinal cord blood flow varied directly with pressure (although autoregulation persisted to an arterial pressure of 40 mm Hg in a few dogs) (95). As with CBF, hypoxia produces vasodilation that overrides both the autoregulation and Pa_{CO_2} effects on CBF. Canine spinal cord blood flow increased sharply when Pa_{O_2} declined to 60 mm Hg and reached a maximum at a Pa_{O_2} of 30–40 mm Hg (96). Hypoxia severely reduces or abolishes the usual vasoconstrictor effect of hypocapnia, and abolishes autoregulation (96). Hypercapnia produces a significant increase in spinal cord blood flow (94–96) and essentially abolishes autoregulation (95). Regional distribution of spinal cord blood flow is not altered significantly by hypoxia, hypercapnia, or hypocapnia (94), however. Although spinal cord blood vessels receive significant sympathetic innervation, they do not appear to respond to chemostimulation or baroreceptor stimulation (94). The electrical stimulation of intact femoral and sciatic nerves produces an increase of 50% in flow to the gray matter of the stimulated area of the cord, presumably by increasing metabolic rate in the affected neurons (94).

Ischemia; Surgical Correction of Thoracic Aortic Aneurysm

Spinal cord gray matter may be quite vulnerable to damage by ischemia (94). The relatively high metabolic rate of actively functioning neurons in the gray matter and the associated flow, together with the susceptibility of the gray matter of the BBB to ischemia, appear to contribute to this vulnerability (94). Whitcomb has noted that damage to the vascular supply of the spinal cord frequently is more harmful than direct intrinsic injury to the cord (97).

The incidence of paraplegia resulting from repair of the descending thoracic aorta has been reported to range from 1 to 11% (98). The neurologic lesion seen often is similar to an anterior spinal artery syndrome that occurs after occlusion of the artery radicularis magna anterior (ARMA) or the artery of Adamkiewicz (99–101). The lesion is manifested by loss of motor function (the large anterior horn cells being partially supplied by the anterior spinal artery), with frequent preservation of sensory function. The ARMA has a variable origin along the spinal cord, arising between T9 and T12 60% of the time, between T5 and T8 14% of the time, and below L1 26% of the time (99,210). Because of the variable origin of the ARMA, it is difficult to predict where this artery arises in a given patient and to design an adequate system of spinal cord protection. That paraplegia is less frequent after repair of atherosclerotic aneurysms than in dissections is believed to be due to the development of collateral circulation in patients with the former condition (102). Similarly, repair of a severely stenotic coarctation of the aorta entails less risk of paraplegia than does a minimal stenosis that has not resulted in extensive collateral circulation.

High cross-clamping of the thoracic aorta results in large increases in afterload and can cause acute left ventricular failure (103,104). Therefore, attempts at preservation of the spinal cord have combined the need to protect the left ventricle with the need to maintain the blood supply of the spinal cord. Left atrial-to-femoral artery (105), right atrial-to-femoral artery (106), and femoral vein-to-femoral artery bypass have been advocated by various investigators to prevent paraplegia, renal failure, and left ventricular failure during cross-clamping of the thoracic aorta. A major problem with these partial bypass procedures is the need for complete anticoagulation, which frequently results in increased postoperative bleeding. Shunts with heparin-bonded tubing (eliminating the necessity for systemic heparinization) have been used between the apex of the left ventricle and the distal aorta (107), as well as from the aorta above the cross-clamp to the aorta below the distal cross-clamp (108). Partial bypass or shunting procedures to preserve spinal cord function have not been successful in preventing paraplegia after aortic cross-clamp, however, possibly because the ARMA is interrupted during surgical repair. Recent reports have indicated that the incidence of paraplegia is similar whether or not adjuncts such as shunts or bypass are used to try to prevent ischemia (98,109–111). When neither a shunt nor bypass is used, hypertension proximal to the aortic cross-clamp can be treated with nitroprusside (98,109) or trimethaphan (98,110).

Berendes et al. (112) recently reported large increases in intraspinal pressure (ISP) during aortic cross-clamping in a patient who was paraparetic after coarctation repair. The ISP increased further during nitroprusside infusion, exceeding the aortic pressure below the cross-clamp. The authors hypothesized that increases in ISP may be a mechanism of paraplegia after aortic cross-clamping. In 1962, Blaisdell and Cooley (115) reported that canine CSF pressure increased with aortic cross-clamping and that removal of CSF prevented paraplegia while elevation of CSF pressure (saline) increased the incidence of paraplegia. They recommended that patients be given urea before aortic cross-clamping so as to minimize CSF pressure elevations seen with aortic cross-clamping.

We may speculate that, because an increase in ISP during aortic cross-clamping may result from increased intracranial blood volume secondary to aortic pressure above the cross-clamping exceeding the upper limit of cerebral autoregulation, lowering the Pa_{CO_2} might minimize this increase in intracranial blood volume. Risks of hyperventilation would include decreased spinal cord blood flow during the period of potential cord ischemia, however. Prophylactic administration of mannitol to decrease brain mass might be reasonable, the risk being that of subdural hematoma due to tearing of diploic veins (113). If the increased ISP reported by Berendes et al. was due to cerebral vasodilation and increased intracranial blood volume, perhaps the nitroprusside dose should be chosen to protect against left ventricular failure rather than arbitrarily to restore arterial pressure to the level present before cross-clamping. Increased perfusion pressure above the cross-clamp can maximize collateral circulation to the spinal cord, but cardiac function (as monitored by ST–T segment, pulmonary artery capillary wedge pressure, and cardiac index) must be maintained within a physiologically acceptable range for the patient. Trimethaphan offers the advantage that ISP elevations might be less than if nitroprusside were used, but with the risk that more severe cerebral metabolic derangement (high-energy phosphates) may occur at comparable degrees of hypotension (114). A direct approach to elevated ISP would be ISP monitoring (for example, with a subdural needle) and removal of CSF, as reported by Blaisdell and Cooley in 1962 in the canine model (115). Because CSF removal in the presence of elevated ISP might be contraindicated, however, CSF would have to be removed prophylactically. Risks of subdural needle placement in a heparinized patient probably are higher than the potential benefits of lowering CSF pressure, in our opinion. If postoperative paraplegia occurred, the less likely possibility of a subdural hematoma at the site of dural puncture would need to be ruled out before the lesion could be assumed to be secondary to spinal cord ischemia that developed during aortic repair.

Intraoperative loss of somatosensory-evoked potentials (SSEP) can predict loss of spinal cord function in man (116). A clinical report by Grundy et al. (17) described pronounced and progressive deterioration in SSEP in a patient undergoing scoliosis repair during placement of Harrington rods, which returned to control when deliberate hypotension was discontinued. SSEP monitoring is widely used now during scoliosis repair. SSEP monitoring during descending thoracic aortic repair has been evaluated in animal models and recommended for routine use in humans (118,119). In animal models, SSEPs cease after only a few minutes of aortic cross-clamping unless a shunt or bypass is used, which precludes the use of SSEPs if these adjuncts are not employed. The clinical value of SSEPs during descending thoracic aortic repair has not been determined to date.

Noting that three patients who had spinal cord damage after coarctation repair were hyperthermic, Crawford and Sade (120) suggested that incidental hyperthermia may be associated with a greater frequency of spinal cord damage.

Based on the limited available information regarding anesthesia management of patients undergoing high thoracic aortic cross-clamping, we recommend the administration of mannitol (0.25–0.5 g/kg) before the placement of the aortic cross-clamp; ECG monitoring of V_5 for signs of myocardial ischemia; monitoring of the pulmonary artery capillary wedge pressure to permit the selection of a nitroprusside dose that will protect the left ventricle while simultaneously supporting perfusion pressure proximal to the cross-clamp; normocapnia; and avoidance of incidental hyperthermia. We do not recommend the use of either routine hypocapnia or subdural needle placement for ISP measurement, because of the risks outlined previously.

Morphine

The intravenous administration of morphine (1 mg/kg) reduced canine spinal cord blood flow to 77 ± 13% ($P < 0.01$) and 73 ± 12% ($P < 0.05$) of control (normoxia, < 0.5% halothane) at 30 and 60 min, respectively (43). (It is interesting that similar changes occurred in CBF). The intravenous administration of naloxone (40 μg/kg) 60 min after the morphine returned spinal cord blood flow to control values. Naloxone (40 μg/kg) administered before morphine (1 mg/kg) did not produce any significant change in spinal cord blood flow, but did block the effect of the morphine on spinal cord blood flow. MAP and heart rate decreased significantly to 83% and 57–60%, respectively, of control values after the morphine was administered, whether the morphine was administered before or after the naloxone (43). Spinal subarachnoid administration of 0.2 mg of morphine produced no significant change in spinal cord blood flow (43). Thus the intravenous administration of morphine affects canine spinal cord blood flow (and CBF) via supraspinal opiate receptors (43).

Intracranial Pressure (ICP)

ICP includes both global and regional pressures, although the latter may be difficult to measure (for example, localized pressure around a tumor). It is important to remember that the functional elasticity of the falx cerebri and the tentorium, together with the functional compressibility of the ventricular system (with CSF translocation), may allow a concomitant increase in tissue mass in one intracranial compartment without a global increase in ICP. Physiologically, the ultimate result of increased ICP is ischemia, whether the elevated ICP is regional or global. Ischemia can produce cell damage, leading to patient morbidity or mortality.

Intracranial Contents

Brain tissue, CSF, and intracranial blood comprise the intracranial contents, with brain tissue occupying approximately 80% of the intracranial volume. Being liquids, brain tissue (approximately 80% water), CSF, and blood are incompressible (79). Because of the communications between their intracranial and extracranial compartments, however, CSF and blood can be translocated extracranially (79).

Except for the use of hyperosmotic agents or furosemide (or both) and the effects of anesthesia on cerebral edema, anesthetic management does not significantly alter brain mass, the largest of the three intracranial components. Anesthetic management primarily affects intracranial blood volume. Although a relatively small component of the intracranial contents on a percentage basis, intracranial blood volume can undergo physiologic change more rapidly than can either of the other two components. We have discussed the arterial component of intracranial CBF, including autoregulation, the passive dependence of flow on perfusion pressure when autoregulation is lost, the CBF–$Pa\text{CO}_2$ relationship, and the effects of anesthesia. Increased flow to cerebral veins produces intracerebral venous distention, as noted earlier. Venous distention also can result from obstruction to venous outflow. Extracranial sources of such obstruction include functional stenosis of the jugular vein due to improper positioning of the head and neck, increased intrathoracic pressure (for example, inappropriate ventilatory pattern), coughing or straining (increased intrathoracic pressure, increased intraabdominal pressure, which produces epidural vein engorgement via Batson's plexus), and placing the head lower than the heart.

Cerebrospinal Fluid

CSF is formed at the rate of approximately 0.35 (67) to 0.4 ml/min (121). Approximately 70% of the CSF produced is formed by secretion at choroid plexus tissue located in the roofs of the third and fourth ventricles and the walls of the lateral ventricles (66). The remaining 30% is derived from the capillary bed of the brain and from metabolic water production (which accounts for approximately 12% of the net CSF production, based on $CMRO_2$) (66). CSF formation is an active process, involving at least two enzyme systems, Na^+–K^+-activated ATPase and carbonic anhydrase (66). CSF is formed at a hydrostatic pressure head of approximately 15-cm H_2O, which drives CSF through the ventricular system into the subarachnoid space and spinal canal and provides sufficient hydrostatic pressure to return CSF to blood primarily[5] through the arachnoid villi (66). The arachnoid villi are tubelike structures that protrude from the subarachnoid space into the lumina of the large dural sinuses and spinal dural sinusoids. They function as one-way valves, remaining open only when CSF flows from the subarachnoid space into venous blood and collapsing to obstruct the back flow of blood if venous pressure exceeds CSF pressure (66). CSF flow through the arachnoid villi starts when CSF pressure exceeds venous pressure by approximately 3–6-cm H_2O (66). Although CSF production rate is not limited by ICP unless the latter is quite high, CSF absorption rate does increase with increasing CSF-to-venous pressure gradient (66).

Because no diffusion barrier exists between brain tissue and CSF, either at the pial–glial surfaces or at the ependymal lining of the ventricles, CSF composition rapidly influences the microenvironment of neuronal and glial cells, and hence the operation of the central nervous system (66). CSF composition is both different from and more stable than plasma (Table 3). Factors contributing to the composition of CSF include cellular metabolism, the combination of special transport mechanisms and restricted intracellular diffusion at both the choroid plexus and the cerebrovascular system, and the relative rates of CSF production and reabsorption (66).

Table 3. Concentrations of Various Solutes in Plasma and Lumbar Cerebrospinal Fluid of Human Subjects

Substance	Plasma (mmol)	CSF (mmol)	CSF/plasma
Na	150	147	0.98
K	4.63	2.86	0.62
Mg	3.22	4.46	1.4
Ca	9.40	4.56	0.49
Cl	99	113	1.1
HCO_3	26.8	23.3	0.87
Inorganic P (mg/dl)	4.70	3.40	0.73
Protein (mg/dl)	6,800	28	0.004
Glucose (mg/dl)	110	50–80	0.6
Osmolality	0.289	0.289	1.0
pH	7.397	7.307	—
PCO_2 (mm Hg)	41.1	50.5	—

Modified from Rapoport SI. Blood–brain barrier in physiology and medicine. New York: Raven Press, 1976:50. By permission.

Mammalian animal studies indicate that the choroid plexuses in all four ventricles receive both adrenergic and cholinergic innervation (123). The sympathetic innervation arises in the cervical sympathetic ganglia and inhibits CSF secretion, apparently by combined α-adrenergic vasoconstriction of the choroidal arteries and β-mediated inhibition of CSF secretion (123). Cholinergic muscarinic stimulation also decreases the production rate of CSF, although the site of action has not been defined (123).

Enflurane increases the rate of CSF formation in rats (124) and dogs (125,126). This increased production is compatible with the increased utilization of glucose in the choroid plexus, as reported by Myers and Shapiro (127), and with the decreased sympathetic tone associated with enflurane (124). Enflurane also increases the resistance of CSF outflow in rats (124). The combination of increased CSF production rate and increased resistance to CSF outflow could contribute to the increase in ICP observed in dogs anesthetized with enflurane (128). Canine CSF production rate is decreased by halothane anesthesia and unchanged by isoflurane or fentanyl anesthesia (125). Resistance to CSF outflow reportedly is increased in cats by halothane anesthesia (129). Pentobarbital may enhance CSF reabsorption in the rat (124).

These data from animal experiments suggest that when endeavoring to minimize the increase in intracranial blood volume and net CSF volume, anesthetics such as isoflurane or fentanyl would be preferable to halothane, enflurane, or ketamine (130). Although not yet confirmed in humans, these results are compatible with established clinical data on the effects of various

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[5] Although not yet established in humans or primates, there is growing experimental evidence that some CSF enters the lymphatic system, although the arachnoid villi still are considered the principal CSF drainage pathway (122). Drainage through the lymphatics may become more important when ICP is elevated (122).

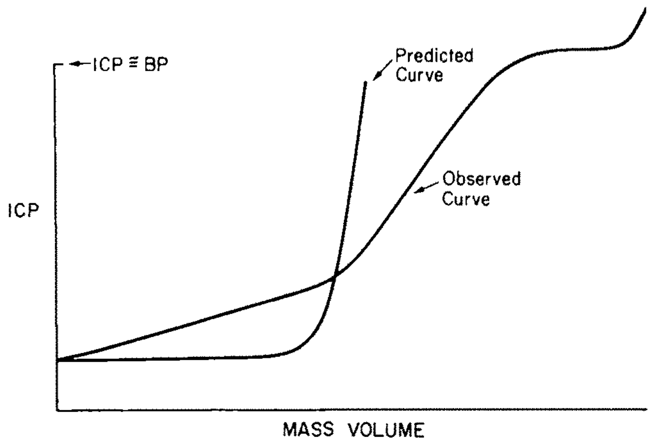

Figure 4. ICP vs mass volume predicted by the Monroe–Kellie doctrine for the curve observed during progressive, epidural balloon inflation in animals. The observed curve is significantly different from the predicted curve in that its initial segment is not flat, but increases slowly to a break point. Beyond this break point, the observed curve is not vertical, but instead increases to a second plateau near the level of arterial blood pressure. (From Miller DJ, Sullivan HG. Severe intracranial hypertension. Int Anesthesiol Clin 1979;17:19–75. By permission of Little, Brown & Company.)

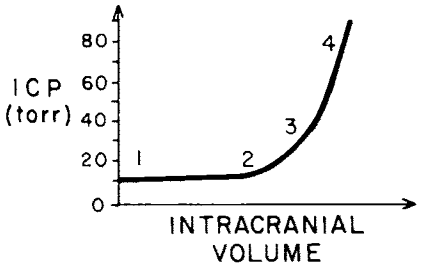

Figure 5. Idealized intracranial volume–pressure relationship. See text. (From Shapiro HM. Intracranial hypertension: therapeutic and anesthetic considerations. Anesthesiology 1975;43:445–71. By permission of JB Lippincott Company.)

anesthetics on ICP in humans. Future studies in humans should be informative.

Intracranial Pressure

The modified Monroe–Kellie hypothesis assumes that the contents of the craniospinal axis cannot be compressed and that their total volume is constant (131). If so, an increase in the volume of one component (brain tissue, CSF, blood volume) would increase ICP unless the volume of one or both of the other components decreased. The curve representing ICP (that is, CSF pressure) vs increasing intracranial volume from a space-occupying lesion would be flat initially, reach a break point representing exhaustion of compensatory mechanisms, and then rise almost vertically (131). Studies indicate that the initial part of the curve is not flat, however, but rises slowly to the break point and then ascends rapidly (but not vertically) to a second plateau approximating arterial pressure (Fig. 4). No single pressure–volume curve represents the whole craniospinal axis. Because of differences in compliance, equal increases in volume in each of the three components do not produce identical increases in ICP; one must specify in which component the volume increase occurs.

For clinical purposes, however, we can utilize an idealized CSF pressure–volume curve (132) (Fig. 5) that is analogous to that portion of the observed curve below the second plateau in Figure 4. The initial portion of this idealized curve (Fig. 5), representing spatial compensation, rises slowly to a break point at which compensatory mechanisms (intracranial-to-extracranial expulsion of CSF and blood) are exhausted, and compliance is reduced. Because compensatory mechanisms are exhausted, each additional increase in volume beyond this break point produces a larger increase in ICP. For a patient with elevated ICP (for example, point 3), any increase in intracranial volume will increase ICP and any decrease in intracranial volume will decrease ICP. In a patient with normal ICP, the point representing the intracranial volume–ICP relationship may occur anywhere on the initial portion of the curve between points 1 and 2. Because a single ICP measurement does not indicate where the patient's representative point lies on this portion of the curve, it is advisable to assume that a patient with a space-occupying lesion but normal ICP is represented by point 2. Any factors that would increase intracranial volume should be avoided, for such an increase in intracranial volume would increase ICP. Before turning to the effects of anesthetic management on the volume of intracranial contents, we again must emphasize that the curve in Figure 5 is an idealized curve. In individual patients, the CSF pressure–volume curve is highly variable and is determined by the interaction of lesion mass and location, the presence or absence of cerebral tissue herniation, CPP, and Pa_{CO_2} (132).

Ekstedt reported that, in supine adult patients, the mean (± SD) lumbar CSF pressure was 10.4 ± 1.4 mm Hg, and did not correlate with the patient's age (121). In supine patients in whom CSF flow from intracranial to spinal subarachnoid space is unimpeded, lumbar CSF pressure referenced to the lateral ventricle may be regarded as representative of intracranial CSF pressure.

Consequences of Increased ICP

To oversimplify, the ultimate consequence of increased ICP is ischemia which, if not corrected, will lead to neuronal damage and subsequent morbidity or mortality.

Intracranial consequences. Progressive increase in ICP eventually leads to decreased CPP, which in turn leads to ischemia. In addition to the potential for neuronal damage, ischemia leads to vasomotor paralysis in the affected area. With regional CBF then passively dependent on CPP, a further decrease in CPP produces more ischemia, more vasomotor paralysis, more neuronal damage, and so forth. It is important to remember that in the presence of intracranial hypertension,[6] a decrease in CPP invariably results in a decrease in rCBF, but an increase in CPP does not necessarily improve flow (131). Increased CPP either can increase intracranial blood volume in other areas, thereby increasing ICP; or can disrupt the BBB, causing cerebral edema, which functionally acts as a mass lesion and increases intracranial hypertension (or it can do both of these). The pathologic cycle involved in progressive elevation of ICP is diagrammed in Figure 6. Ultimately, a progressive increase in ICP will force displacement of brain tissue from the involved area, resulting in herniation (cingulate, tentorial, uncal, cerebellar, or tonsillar) (133). Symptoms and signs of intracranial hypertension are listed in Table 4.

Systemic effects. Cardiovascular, pulmonary, or visceral (or combinations thereof) dysfunction can result from intracranial hypertension and can be a major clinical problem (131) (see Table 4). The vasopressor reponse that accompanies intracranial hypertension may result from distortion of, or focal pressure on, the vasomotor centers in the floor of the fourth ventricle, rather than resulting primarily from direct brainstem ischemia, as originally proposed by Cushing (134) and Kocher (135). It should be emphasized that, although transient vasopressor responses occur in some patients with elevated ICP, such responses are not inevitable. Intracranial hypertension can occur without systemic hypertension (and vice versa) (131). The effector "limb" in the vasopressor response is the sympathetic nervous system. Evidence from animal studies suggests that the systemic hypertensive response also may be triggered by inadequate supratentorial perfusion (136) and that bradycardia, arrhythmias, pupillary changes, and increased pulse pressure may precede systemic hypertension, with bradycardia being a fairly consistent early sign (136).

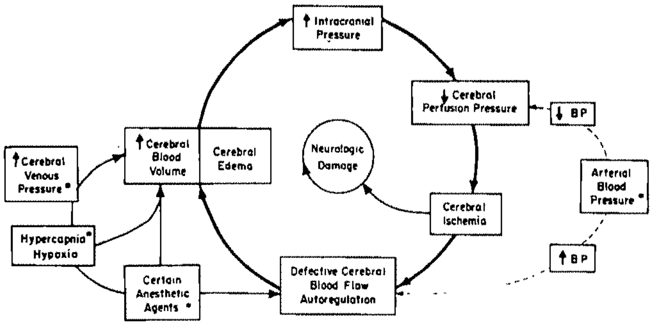
↑ Intracranial Pressure
↓ Cerebral Perfusion Pressure
↓ BP
Arterial Blood Pressure *
↑ BP
Cerebral Ischemia
Neurologic Damage
Defective Cerebral Blood Flow Autoregulation
Certain Anesthetic Agents *
Hypercapnia* Hypoxia
↑ Cerebral Venous Pressure *
↑ Cerebral Blood Volume
Cerebral Edema

Figure 6. Pathophysiology of uncontrolled intracranial hypertension. Cycle elements potentially under the control of the anesthesiologist are indicated by asterisks. (From Shapiro HM. Intracranial hypertension: therapeutic and anesthetic considerations. Anesthesiology 1975;43:445–71. By permission of JB Lippincott Company.)

The bradycardia that frequently accompanies systemic hypertension is vagally mediated (131). Atrial and ventricular arrhythmias, various degrees of atrioventricular block, ECG changes consistent with myocardial infarction, and subendocardial hemorrhage have been associated with intracranial hemorrhage or other severe brain insults (131,137)

At least three forms of respiratory dysfunction can occur: variation in respiratory pattern, neurogenic pulmonary edema, and adult respiratory distress syndrome. All three eventually result in hypoxia, which then increases the magnitude of intracranial hypertension and tissue damage (131). Variations in respiratory pattern can range from hyperventilation to apnea. It is apnea, not cardiac arrest, that is the primary cause of death in patients whose condition progresses through tentorial and tonsillar herniation (131). Neurogenic pulmonary dysfunction presents a spectrum of pulmonary pathophysiologic changes ranging from severe pulmonary edema to mild $\dot{V}/\dot{Q}$ mismatch. Neurogenic pulmonary edema is relatively rare and is more common in teenagers and young adults (131). The definitive mechanism is not known (131,132). Theories have included sudden increases in central blood volume and pulmonary venular spasm (132).

For a discussion of visceral dysfunction associated with intracranial hypertension, the reader is referred to Miller and Sullivan (131). Other signs of intracranial hypertension are listed in Table 4.

Effects of Anesthetic Agents

In patients with space-occupying lesions, transient but potentially large increases in ICP induced by halothane can be minimized or abolished by inducing hypocapnia prior to administering halothane (138). The simultaneous introduction of halothane and ini-

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[6] Mean CSF pressure (mm Hg) measured from the ventricular or supratentorial space (131): mean ICP ≤ 10 = normal; mean ICP ≥ 20 = definitely abnormal; and mean ICP 10–20 = suspicious.

Table 4. Signs of Intracranial Hypertension

Produced by increased ICP alone	Produced by local brain damage or distortion	Produced by total brain ischemia
Headache	Headache	Unconsciousness
Vomiting	Vomiting	Bilateral, fixed dilated pupils
Papilledema	Drowsiness	Absent brainstem reflexes
Drowsiness	Decerebrate rigidity	Arterial hypertension
	Oculomotor palsy	Apnea
	Impaired or absent brainstem reflexes	
	Arterial hypertension	
	Bradycardia	
	Abnormal respirations	
	Apnea	

From Miller JD, Sullivan HG. Severe intracranial hypertension. Int Anesthesiol Clin 1979;17:19–75. By permission of Little, Brown and Company.

tiation of hyperventilation did not consistently prevent the increase in ICP (138).

In contrast, the simultaneous initiation of hyperventilation and administration of isoflurane prevented increased ICP for patients with intracranial mass lesions (139). Nevertheless, recognizing individual patient variability, it would be prudent to induce hypocapnia before administering isoflurane to patients with intracranial mass lesions (139). The same advice would apply to the use of enflurane, with the precaution that pronounced hypocapnia and high concentrations of enflurane should be avoided because of the attendant potential for inducing seizure activity.

Reports of the effects of N_2O on ICP are contradictory (140). In patients with normal ICP, no increase in lumbar CSF pressure was noted when N_2O was administered (140). Significant increases in ICP over control values were observed when 50% N_2O was administered to patients with head injury; the authors emphasized that their results do not contraindicate the use of N_2O in head-injured patients but do suggest that hypocapnia be induced first (140).

As discussed in an earlier section, barbiturates decrease $CMRo_2$, resulting in a decrease in CBF. To the extent that they thereby decrease intracranial blood volume, they decrease ICP. This effect of barbiturates on ICP enjoys wide clinical application. Thiopental or diazepam (or both) can block the effect of 70% N_2O on ICP (141).

In the absence of secondary increases in $Paco_2$ due to respiratory depression, narcotics tend to prevent an increase in ICP or to reduce ICP. Intravenously administered fentanyl (0.2 mg) produced small clinically and statistically insignificant changes in ICP in 10 patients who had intracranial space-occupying lesions, and was considered a valuable adjuvant to the N_2O–O_2–relaxant anesthetic regimen (142). Innovar (1 ml per 9–11.4 kg of body weight), followed by fentanyl (0.05 mg every 15–45 min), did not increase ICP in 10 hypocapnic patients with space-occupying lesions (138).

The effects of anesthetic agents are summarized in Table 5.

Intrathoracic, Intraabdominal Pressure; Coughing; Tracheobronchial Suction

The effects of intrathoracic and intraabdominal pressure on cerebral venous drainage were noted earlier (see the intracranial contents section above). When controlled positive-pressure ventilation is used, an appropriate ventilatory pattern that minimizes an increase in mean intrathoracic pressure is essential.

Coughing or straining increases ICP by increasing the cerebral venous pressure and distention, or intracranial CSF, or both. Increased intrathoracic pressure interferes with cerebral venous drainage. Increased intraabdominal and intrathoracic pressures transmitted to the epidural veins via Batson's plexus cause engorgement of epidural veins, which in turn compress the spinal subarachnoid space, resulting in translocation of CSF intracranially. It is essential that muscle relaxation sufficient to prevent diaphragmatic movement be achieved before intubation in patients in whom regional or global increases in ICP are to be avoided. Control of blood pressure during induction and intubation also is essential to prevent untoward increase or decrease in MAP and hence CPP, as discussed in an earlier section.

During suctioning of the tracheobronchial tree, tracheal stimulation occurs during a brief apneic period. Response to the tracheal stimulation, or an increase in CBF due to an increase in $Paco_2$ during apnea, or

Table 5. Effects of Anesthetic Drugs and Techniques on Blood Pressure, Intracranial Pressure, and Cerebral Perfusion Pressure[a]

	Blood pressure	Intracranial pressure	Cerebral perfusion pressure[b]
Technique			
Hyperventilation	↓	↓	↑
Hypothermia	↓	↓	– ↓
Agents			
Inhalation			
Volatile[c]	↓	↑	↓
Nitrous oxide	–	↑	↓
Intravenous			
Ketamine	↑	↑	↓
Fentanyl	↓	↓	– ↑
Droperidol	↓	↓	– ↑
Diazepam[d]	– ↓	? ↓	?
Thiopental	– ↓	↓	↑
Muscle relaxants			
d-Tubocurarine[e]	↓	↑	↓
Pancuronium[e]	–?	?– ↓	–?

[a] Clinically significant effects at commonly effective anesthetic or sedative doses are indicated. The resulting CPP direction of change depends not only on the BP and ICP directions but also on the magnitude of the change. Ventilation is assumed stable and controlled.

[b] Cerebral perfusion pressure = blood pressure – intracranial pressure.

[c] Halothane, methoxyflurane, fluroxene, and enflurane.

[d] Diazepam predicted from available CBF data.

[e] Pancuronium is assumed to be less potent in histamine-releasing properties than *d*-tubocurarine. Muscle relaxant effects in the table refer to actions immediately after their intravenous administration.

Modified from Shapiro HM. Intracranial hypertension: therapeutic and anesthetic considerations. Anesthesiology 1975:43, 445–471. By permission of JB Lippincott Company. Refer to Figure 1 for meaning of symbols.

both, could result in an increase in ICP. Fisher et al. (143) reported that, in 9 children with brain injury (baseline ICP ≥ 12 mm Hg), the increase in ICP during endotracheal suctioning was due to tracheal stimulation and not to increased $Paco_2$ during apnea. Hemodynamic and ICP changes due to tracheal stimulation have been blunted by intravenously administered lidocaine or thiopental in patients who had received muscle relaxants. Based on their study in 15 comatose, nonparalyzed patients, White et al. (144) suggest that the combined use of topical anesthesia and a neuromuscular blocking agent may be required to prevent the ICP elevation or the MAP increase (or both) associated with endotracheal suctioning (Table 6). Intravenously administered fentanyl (1 μg/kg), thiopental (3 mg/kg), and lidocaine (1.5 mg/kg) all failed to prevent increased ICP after suctioning, although the latter two drugs produced initial decreases in ICP of 4–6 mm Hg. When instilled into the trachea, lidocaine (1.5 mg/kg) attenuated the increase in ICP associated with suctioning but provoked a cough response and an initial increase in ICP. Hamill et al. (145) reported that, in patients with brain tumors, intravenously administered lidocaine (1.5 mg/kg) prevented the increase in ICP that was associated with intubation, while laryngotracheal spray (2 ml of 4% lidocaine) did not.

Anesthetic Management of a Patient With Increased ICP

Induction. Several factors must be considered when formulating the plan for inducing anesthesia in a patient with overt or potential intracranial hypertension. Maneuvers that would increase sympathetic nervous system activity (for example, placing the mask on the face of an apprehensive child) should be avoided. Selection of agents that decrease $CMRo_2$, CBF, and intracranial blood volume is desirable (for example, barbiturates, narcotics, etomidate). Hypocapnia should be induced as soon as possible during the induction. Adequate depth of anesthesia, together with intravenous lidocaine (1–1.5 mg/kg), will blunt the sympathetic nervous system response to laryngoscopy and tracheal intubation. Adequate muscle relaxation is necessary to prevent coughing, bucking, or straining during and subsequent to tracheal intubation. Maintenance of CPP within the patient's preoperative range is critical. Note that this discussion concerns the induction of general anesthesia in a patient with overt or potential increased ICP. These remarks should not be interpreted to mean that volatile agents are contraindicated in these patients. We use volatile agents with or without intravenous narcotic supplement for maintenance of anesthesia when we think this is the

Table 6. Cough Scores, Baseline ICP and MAP Values (mm Hg), and Mean Changes (mm Hg) during and immediately after Endotracheal Suctioning (± SEM)

Treatment	Cough score	Base ICP	Peak Δ ICP	Post Δ ICP	Base MAP	Peak Δ MAP	Peak Δ CPP
Normal saline (2 ml)	3.0	15 ± 1	+ 22	+ 9	101 ± 7	+ 27	+ 5
	(± 0.1)		(± 3)	(± 2)		(± 3)	(± 1)
Fentanyl (1 μg/kg)	2.8	13 ± 1	+ 14	+ 1[a]	100 ± 6	+ 30	+ 16
	(± 0.1)		(± 2)	(± 1)		(± 5)	(± 3)
Thiopental (3 mg/kg)	2.8	12 ± 1	+ 20	+ 7	99 ± 6	+ 28	+ 8
	(± 0.1)		(± 3)	(± 2)		(± 4)	(± 2)
Intravenous lidocaine (1.5 mg/kg)	2.7	16 ± 2	+ 19	+ 4	102 ± 9	+ 28	+ 9
	(± 0.1)		(± 3)	(± 2)		(± 2)	(± 2)
Intratracheal lidocaine (1.5 mg/kg)	2.0[a]	15 ± 1	+ 11[a]	+ 4	99 ± 6	+ 22	+ 11
	(± 0.2)		(± 2)	(± 2)		(± 3)	(± 2)
Succinylcholine (1 mg/kg)	1.2[b]	16 ± 2	+ 3	0[a]	104 ± 6	+ 17	+ 14
	(± 0.1)		(± 2)	(± 1)		(± 2)	(± 2)

Significantly different from control (normal saline): [a]$P < 0.05$; [b]$P < 0.01$.

From White PF, Schlobohm RM, Pitts LH, Lindauer JM. A randomized study of drugs for preventing increases in intracranial pressure during endotracheal sunctioning. Anesthesiology 1982;57:242–4. By permission of JB Lippincott Company.

best choice for the patient's general medical and surgical condition. When using volatile agents, we induce hypocapnia before introducing the agent, maintain CPP, and are guided in our agent selection by our awareness of the relative effects of halothane, enflurane, and isoflurane on $CMRO_2$, CBF, and CSF dynamics.

For a child frightened of having an intravenous needle inserted, a smooth induction with a volatile agent may be a better alternative than having the child struggle and cry in response to the intravenous insertion of a cannula. Once the child is anesthetized sufficiently to allow placement of the cannula, barbiturates or narcotics can be administered.

Fluid Balance

Fluid composition and volume can affect intracranial volume and hence ICP. Although decisions regarding the composition and volume of intravenously administered fluids depend on the patient's general condition and the operative procedure, from the standpoint of the craniospinal axis the intravenous infusion of 5% dextrose–water is potentially dangerous if its rate of administration exceeds the rate at which water is lost (113). After the initial distribution of glucose throughout the total body water, the glucose level decreases more rapidly in blood than in the brain or spinal cord. Water, therefore, moves from the relatively hypotonic plasma into the brain, spinal cord, and CSF, thereby potentially increasing ICP or producing cerebral or spinal cord edema (or both). Administering 5% glucose in a balanced salt solution minimizes this problem, because of the residual intravascular osmotic effect of the salt molecules. The approximate osmolality, composition, and pH of a few crystalloid solutions for intravenous use are listed in Table 7.

Cerebral Edema

Types. Cerebral edema may be divided into three types (133): vasogenic, cytotoxic, and interstitial. In vasogenic edema, the most common type, increased capillary permeability permits leakage of plasma filtrate primarily into white matter. Vasogenic edema is associated with brain tumors, abscesses, infarctions, head trauma, hemorrhage, and purulent meningitis (133). In cytotoxic edema, all the cellular elements of the brain or spinal cord may swell (133). This is an intracellular form of edema, in contrast to the primarily extracellular vasogenic edema. Two clinical conditions characterized by cytotoxic edema are acute hypoosomolality (for example, water intoxication) and cerebral edema due to cerebral hypoxia. Interstitial edema results from obstructive hydrocephalus and involves increased water and sodium content in the periventricular white matter.

Hyperosmolar Agents, Loop Diuretics. In 1958, Javid (146) introduced the use of hypertonic nonelectrolyte solutions to extract water acutely from brain tissue. Hyperosmolar agents decrease intracranial volume by decreasing water content in normal brain tissue (79,131). To be effective, a hyperosmolar agent must be delivered to the target organ or tissue; must not leak into the tissue but rather be contained within the plasma by a membrane impermeable to the agent (for example, the BBB); must increase plasma osmolality relative to tissue osmolality; and must undergo renal

Table 7. Composition of Crystalloid Solutions[a] Available for Clinical Use

	Ringer's lactate	5% Dextrose in Ringer's lactate	5% Dextrose in water	0.9 NaCl	5% Dextrose in 0.45 NaCl	5% Dextrose in 0.2 NaCl
pH (approx)	6.5	5.0	4.0	5.0	4.0	4.0
Osm (mosm/L) (approx)	272	524	252	308	406	321
Na (mEq/L)	130	130	None	154	77	34
K (mEq/L)	4	4	None	None	None	None
Ca (mEq/L)	3	3	None	None	None	None
Cl (mEq/L)	109	109	None	154	77	34
Glucose (g/dl)	None	5	5	None	5	5
Lactate (mEq/L)	28	28	None	None	None	None

[a]These figures obtained from fluids supplied by Travenol Laboratories, Deerfield, IL.

glomerular filtration without significant tubular reabsorption (123,133). Ideally, the agent also should not irritate vascular and other tissues and should be pharmacologically inert. To date the ideal agent has not been found.

By decreasing intracranial volume through extraction of water primarily from normal brain tissue, hyperosmotic agents can decrease elevated ICP acutely, thereby improving CPP and promoting flow to the hypoperfused tissue. Hyperosmotic agents are useful in vasogenic edema, may help acutely in hypoosmolality, but are not helpful in interstitial edema (133).

MANNITOL. Mannitol is the most commonly used hyperosmolar agent, because it is relatively effective and safe (79). Although doses between 0.5 and 2.0 g/kg have been utilized (79), Marshall et al. (147) reported that 0.25 g/kg produced decreases in ICP equivalent to those produced by 0.5 or 1 g/kg in eight patients with acute head injury and increased ICP. Osmotic gradients approximating 10 mosm produced satisfactory reduction in ICP (147), although previous reports had suggested that higher gradients may be required (133).

UREA. Urea, used as an hyperosmolar agent in the past, currently is not widely used. Problems associated with its use included the rebound phenomenon and tissue irritation.

POTENTIAL COMPLICATIONS. Potential complications of the use of hyperosmotic agents include rebound of elevated ICP, hyperosmolality, electrolyte loss, and changes in blood viscosity and coagulation (148). Rebound or secondary elevation of ICP can result from leakage of molecules of the hyperosmotic agent into neuronal tissue, retention of these molecules after diuresis has decreased plasma concentration of the agent, and translocation of plasma water into neural tissue due to the resultant residual osmotic gradient. Experimentally, this rebound can be prevented by replacing only one-third of the urine volume excreted during the osmotic diuresis (132). Metabolic acidosis and renal failure are almost certain to occur at plasma osmolalities above 350 mosm/L and may occur at osmolalities above 320 mosm/L (131). With regard to relative osmolalities, it is important to remember that, given the choice of preserving volume or intracellular osmolality in response to plasma hyperosmolality, the brain will preserve volume, and intracellular osmolality will approach plasma osmolality (133). Therefore, acute reduction in brain volume can be achieved with hyperosmotic agents, but the repeated administration of these agents is less useful (and potentially harmful).

Hyperosmotic agents should not be given to patients with overt or potential congestive heart failure (79,132), impaired renal function (79,132), or high hematocrit values. The transient hypervolemia induced by the agents is hazardous in patients with cardiac decompensation. Diuresis-induced increase in blood viscosity can produce "sludging" and thrombosis in patients with high hematocrit values; very careful fluid replacement is required. Hypovolemia should be avoided.

LOOP DIURETICS. Furosemide has been used experimentally and clinically to reduce ICP (79,132,148). In patients anesthetized with halothane–N_2O–O_2 for craniotomy, furosemide (1 mg/kg) reduced ICP without producing the increase in serum osmolality or the decreases in serum Na^+ and K^+ concentrations observed after the administration of 1 g/kg of mannitol (148). (A note of caution: very small doses of furosemide, such as 5–10 mg intravenously, frequently produce a large diuresis under general anesthesia; it is best to start with 5–10 mg intravenously and give supplemental doses if adequate diuresis and decreases in ICP are not obtained initially.) Although ethacrynic acid decreased ICP in experimental studies, we are unaware of significant clinical experience using it for this purpose.

OSMOTIC PLUS LOOP DIURETICS. Compared with mannitol (1.4 g/kg) alone, a 20-min infusion of mannitol (1.4 g/kg) plus furosemide (0.3 mg/kg) in anesthetized patients (N_2–O_2–thiopental–fentanyl) produced a greater volume and rate of water loss, and a greater, more consistent and more sustained brain shrinkage (149). However, hyperosmolality, hyponatremia, and hypochloremia also were significantly greater ($P < 0.05$) and more sustained with the mannitol–furosemide combination (149). Replacement of the Na^+ and Cl^- loss improved the more noticeable lethargy exhibited during the early postoperative hours by the patients who had received the mannitol–furosemide treatment (149).

In experimentally induced intracranial hypertension (epidural balloon) in anesthetized animals, the combination of mannitol (0.75 g/kg (150), 1.0 g/kg (151)) and furosemide (0.7 mg/kg) produced a more rapid, greater, and more sustained decrease in ICP than did either agent alone. Of the various mechanisms proposed for the synergistic action of mannitol and furosemide, the renal effects of the loop diuretics remain the most likely primary mechanism (150,151). Reports of the effectiveness of furosemide alone in the treatment of intracranial hypertension have been conflicting (150).

Brain Protection

Brain protection can be defined as prevention or amelioration of the neuronal damage occurring after an hypoxic or ischemic event. Both hypoxia and ischemia decrease O_2 delivery to the brain by either reduced O_2 tension (hypoxemia) or a pathologic decrease in CBF (ischemia), as discussed previously. Because the pathophysiology in each of these forms of reduced O_2 delivery is different, therapeutic interventions that provide protection in one form should not be assumed to be effective in other forms. In hypoxemia, the only effective compensatory mechanism is increased CBF, whereas in incomplete ischemia, the outcome depends largely on the relationship between residual perfusion (O_2 delivery) and O_2 demand. We will discuss the major therapies that have been effective in at least one form of hypoxia or ischemia; these include hypothermia, barbiturates, other anesthetics, and the calcium entry blockers.

Hypothermia

The capacity of hypothermia to protect the brain during periods of decreased or absent O_2 delivery is well-known and is used daily in cardiac operating rooms. The magnitude of the protection is proportional to the decrease in temperature, because cerebral metabolic rate decreases as temperature decreases. This relationship between temperature and metabolism is expressed by the temperature coefficient (Q_{10}), which is defined as the ratio of the rates of O_2 metabolism at two temperatures separated by 10°C. The Q_{10} value for cerebral metabolism for the temperature range 27–37°C is 2.2, indicating that cerebral metabolic rate at 37°C is 2.2 times that at 27°C (152).

Hypothermia decreases the rates of all biochemical reactions, including those related to both components of $CMRo_2$ (neuronal function and cellular integrity). This reduced O_2 demand renders the cells more tolerant of reduced O_2 delivery. Hypothermia is effective in reducing cerebral metabolism whether or not neuronal electrical acitivity has been abolished by complete global ischemia. This is in contrast to general anesthetics, which affect only that portion of cerebral metabolism related to neuronal electrical activity.

However, hypothermia as a means of brain protection is not practical in most circumstances. Cardiopulmonary bypass is necessary to achieve adequate cooling and to provide circulation when the heart fibrillates at 26–28°C. Metabolic acidosis is common because of inadequate flow rates, prolonged circulatory arrest, and temperature gradients between core and peripheral tissues. Oxygenation may be difficult owing to the changes in the oxyhemoglobin dissociation curve and O_2 solubility that occur at lower temperatures. Aggregation or sludging of red blood cells and alterations in blood coagulation also may occur, as may complications of systemic heparinization.

Barbiturates

Barbiturates, discussed in an earlier section, have been used for sedation, hypnosis, seizure control, and as a component of general anesthesia. Several CNS depressants (anesthetics) can prolong survival time in hypoxic or asphyxiated animals (14,153)—a crude measure of brain protection. Barbiturates appear to offer the greatest protection in this model of incomplete global ischemia (154,155). The major mechanism of action is presumed to be improvement of the ratio of O_2 supply to O_2 demand. As noted previously, high doses of barbiturates can reduce $CMRo_2$ to 40% of control (31). Unlike hypothermia, barbiturates reduce only the portion of $CMRo_2$ that is related to neuronal electrical activity. Therefore, they might provide protection in instances of incomplete global ischemia in which some basal nutrient supply to cerebral tissues is maintained. Barbiturates also can suppress catecholamine-induced brain hypermetabolism and suppress seizure activity and its associated increased metabolic rate, again improving the ratio of O_2 delivery to demand.

Barbiturates also have been shown to provide some brain protection in experimental focal ischemia, that is, models of stroke. Treatment with high-dose barbiturates before, or as long as 30 min after, an ischemic event have been effective in decreasing neurologic and neuropathologic deficits (156–159). The protective action of the barbiturates in experimental focal ischemia may be due to a reduction in cerebral metabolic demand and vasoconstriction of normal cerebral vessels, which may improve the distribution of CBF to diseased areas in which vasomotor paralysis is present. Barbiturates also decrease cerebral edema and the secretion of CSF which may contribute to injury in focal ischemia (160,161). Unfortunately, the effectiveness of the barbiturates in humans after strokes has not been demonstrated.

In humans, barbiturates decrease ICP (162) and have been used in patients with abnormally high ICP (163) during surgery (164) or as the result of head trauma (165), encephalitis, or Reye's syndrome (166). As vasoconstrictors, the barbiturates decrease ICP by increasing cerebrovascular resistance and decreasing cerebral blood volume (167). In patients with elevated ICP, barbiturate-induced reductions were greatest when the initial ICP was abnormally high; an increase in CPP often accompanied the decrease in ICP. Reduction in ICP appeared to improve survival in patients with head injury or encephalitis but not in those with stroke (163).

There are no confirmed studies that barbiturates provide protection after complete global ischemia, as in models of cardiac arrest (Table 8). One promising study that demonstrated improved neurologic recovery in dogs treated with pentobarbital before complete cerebral ischemia (produced by occlusion of the ascending aorta and venae cavae) (168) could not be repeated by other investigators (169). Another report that massive doses of thiopental given to primates after 16 min of complete cerebral ischemia (produced by systemic hypotension and neck tourniquet inflation) could decrease the incidence and severity of neuropathologic abnormalities and improve neurologic function (170) could not be confirmed by the same laboratory (171), and the authors could not support the use of barbiturates for brain resuscitation (171). Others, using a ventricular fibrillation model to produce complete cerebral ischemia in cats, also failed to demonstrate barbiturate protection (172). Interestingly, however, this study did demonstrate that severe neurologic deficit correlated with the presence of an abnormal EEG, which may have reflected increased cerebral energy expenditures at a time when postischemic cerebral hypoperfusion existed (173). Cerebral hypoperfusion has been reported to last at least 18 hours (dogs) (174). It is presumed that any sudden increases in energy demands during this period of hypoperfusion may not be matched by comparable increases in O_2 delivery, resulting in further ischemic brain damage. Perhaps suppression of such hyperactivity during this period by barbiturates, diazepam, or phenytoin might improve a patient's recovery from a severe ischemic insult (175). The only clinical study in which barbiturates were administered after cardiac arrest failed to demonstrate any more protection from barbiturates than from conventional therapy (176). Because none of the studies demonstrating barbiturate protection during complete global ischemia can be confirmed, none of the proposed mechanisms such as inhibition of lipid peroxidation (177) or free radical scavenging (178–180) can be confirmed.

Table 8. Protection by Barbiturates in Complete Global Ischemia

Study	Species	Method of ischemia	Protection
Goldstein et al. (168)	Dog	Vessel ligation	Yes
Steen et al. (169)	Dog	Vessel ligation	No
Bleyaert et al. (170)	Primate	Choke	Yes
Gisvold et al. (171)	Primate	Choke	No
Todd et al. (172)	Cat	Fibrillation	No

Isoflurane

Although the barbiturates are the most potent pharmacologic depressants of cerebral metabolism, most anesthetics also produce some cerebral metabolic depression, as discussed in an earlier section. Isoflurane produces a dose-related decrease in $CMRo_2$ until an isoelectric EEG is produced, at which point the cerebral metabolic profile is normal. Compatible with this cerebral effect of isoflurane is the report that in two animal models of incomplete global ischemia, isoflurane provided cerebral protection similar to that demonstrated for the barbiturates (181). The mechanisms proposed for this protection include metabolic depression secondary to a reduction in cortical electrical activity and suppression of hypoxic convulsions.

Calcium Entry Blockers

During the past few years, interest has focused on calcium entry blockers for the treatment of complete global cerebral ischemia. Physiologic events occur in the postischemic period which, if treated, might improve neurologic recovery. Cerebral hyperperfusion

Table 9. Protection by Calcium Entry Blockers in Complete Global Ischemia

Study	Species	Method of ischemia	Agent	Protection
White et al. (188)	Dog	Cardiac arrest	Flunarizine	Yes
Newberg et al. (63)	Dog	Vessel ligation	Flunarizine	No
Winegar et al. (189)	Dog	—	Lidoflazine	Yes
Vaagenes et al. (192)	Dog	—	Lidoflazine	No
Steen et al. (184)	Dog	Vessel ligation	Nimodipine	Yes
Steen et al. (197)	Dog	Vessel ligation	Nimodipine	?
Hoffmeister et al. (198)	Cat	Neck tourniquet	Nimodipine	Yes

occurs in the first 10–20 min after restoration of blood flow. This transient hyperperfusion is associated with vasomotor paralysis, may cause breakdown of the BBB and consequent edema formation, and is followed by a prolonged period of hypoperfusion (CBF is approximately 25% of control value) (174,175,183). Proposed mechanisms for this hypoperfusion include coagulation abnormalities, rheologic disorders, microvascular endothelial swelling, accumulation of vasoactive peptides, or vasospasm secondary to abnormal potassium or calcium ion flux. Suggested therapeutic approaches include anticoagulants, hemodilution, or relief of vasospasm. Biochemical derangements occurring after complete global ischemia include depletion of high energy phosphate compounds (which, however, are quickly restored with reestablishment of perfusion), formation of reactive free radicals, abnormal fatty acid metabolism (177), defective protein synthesis, and increases in intracellular calcium levels (183).

Because they may ameliorate the postischemic hypoperfusion (184) and reduce abnormal fatty acid metabolism (185), calcium entry blockers are being investigated for their role in brain protection. Several calcium entry blockers are potent cerebral vasodilators (186,187). Although initial studies demonstrated that flunarizine (188) and lidoflazine (189) could ameliorate the postischemic hypoperfusion state, thereby improving neurologic recovery, these findings have not been confirmed (190–192) (Table 9).

Nimodipine is the most promising calcium entry blocker for possible brain protection. Nimodipine increases total cerebral blood flow in normal cats, dogs, rabbits, and primates without increasing cerebral metabolism (193–196). In a dog model of complete global ischemia (ligation of ascending aorta and venae cavae), nimodipine given either before or after 10 min of ischemia partially corrected the postischemic hypoperfusion state (in which CBF averaged 39–46% of control value) (184,197). Improved neurologic outcome after complete global ischemia has been reported in cats (198) and dogs (184) pretreated with nimodipine. Primates treated with nimodipine after 17 min of complete global ischemia (systemic hypotension plus neck tourniquet) also demonstrate normal or improved neurologic function (211).

Nimodipine also has a beneficial effect on cerebral vasospasm in humans after subarachnoid hemorrhage (199), and increases CBF in humans with cerebrovascular disease (200). However, these promising results demonstrating some brain protection with nimodipine must be accepted with caution. The initial studies with barbiturates cannot be confirmed. Although, in similar animal models, nimodipine has demonstrated improved neurologic recovery whereas the barbiturates did not, confirmation of the nimodipine studies is necessary before they can be accepted. A recent study in a primary focal ischemia model (middle cerebral artery occlusion) demonstrated that nimodipine produced higher residual CBF, but abolished autoregulation and CO_2 responsiveness and produced cerebral edema and disturbances of ion homeostasis at higher blood flow, thereby possibly rendering the cerebral tissues more susceptible to ischemia (193).

Other Agents

Phenytoin has provided cerebral protection in several animal models. The cerebral protection is not due to a decrease in cerebral metabolic rate. Proposed mechanisms include stabilization of membranes, thereby slowing the release of potassium or influx of calcium into ischemic cells (201).

Midazolam maleate, a new benzodiazepine, also has been shown to provide some limited protection in animal models of hypoxia. Midazolam is a potent depressant of cerebral metabolic rate to 55% of control and does not produce the severe hemodynamic depression seen with thiopental (35).

It has been stated that intravenously administered lidocaine might provide some protection to the ischemic brain (202). Like hypothermia, lidocaine can delay the potassium efflux from the brain cortex during ischemia. As a local anesthetic, lidocaine blocks the sodium channels in the cell and therefore can at least partially block the leak of ions from the cell. If the hypothesis that a delay in ischemic metabolic changes implies a delay in the appearance of irreversible cell damage is correct, then lidocaine might provide protection. In addition, lidocaine can depress cortical electrical activity, thereby decreasing cerebral metabolism, and can block CNS hyperactivity (that is, seizures) and their attendant increased metabolic state.

Etomidate, which decreases both CBF and $CMRO_2$ in humans, has provided limited cerebral protection in several animal models of ischemia (203,204). As with the other anesthetics, the presumed mechanism of action is a decrease in cortical electrical activity producing a decrease in cerebral metabolic rate and hence a decrease in cerebral O_2 demands at a time when there is reduced O_2 delivery.

Anesthetic Management for Nonneurosurgical Procedures in Patients with Head or Spinal Trauma

Neurologic trauma is an ubiquitous problem. During a recent 2-yr period, 13% of the 2769 emergency surgical procedures at one of our affiliated hospitals were neurosurgical. A patient with a nonsurgical neurologic problem who requires surgery for other trauma-related disorders presents the anesthesiologist with the challenge of providing appropriate anesthesia without impairing the patient's neurologic condition. Exemplifying this anesthetic situation are patients with closed-head injuries or spinal injuries.

Intracranial Volume, Pressure

The pressure volume curve for intracranial compliance has been presented elsewhere in this article. Some cerebral edema is probable in a patient who has suffered a cerebral contusion or more serious cerebral injury. The degree of cerebral edema may be estimated from a computed tomographic scan. As in patients with brain tumors or other intracranial mass lesions, the potential for brain herniation exists in four areas: transcalvarial (through the skull); cingulate (across the falx cerebri); temporal (uncal, through the tentorium cerebella); and cerebellar (through the foramen magnum) (133). Monitoring of ICP may be indicated. The anesthesiologist must be cognizant of the potential for rapid increases in ICP during anesthesia, unless appropriate preventive measures are taken, as discussed previously.

Systemic Effects of Increased ICP

A search should be made for systemic signs of increased ICP (outlined earlier) in the preanesthetic evaluation of patients with closed-head trauma. Confusion, delirium, restlessness, and hyperventilation can precede stupor and coma (205). Bradycardia and hypertension can signify brainstem compression. ST-segment and T-wave electrocardiographic changes can mimic myocardial ischemia. Various degrees of neurogenic pulmonary dysfunction can occur.

Anesthetic Management

As noted previously, the presence of overt or potential intracranial hypertension requires an anesthetic technique that will avoid increasing the intracranial blood volume while maintaining CPP and adequate perfusion. Hypoxia, CO_2 retention, hypertension, hypotension, and coughing or straining (or both), as well as certain anesthetic techniques and drugs, can cause rapid neurologic deterioration in a patient with a closed-head injury. Appropriate choice of anesthetic agents and ventilatory pattern is required. Our general plan for these patients includes hypocapnia, avoiding cerebral vasodilating agents unless they are indicated for systemic reasons, and control of MAP to maintain CPP.

Avoidance of hypercapnia is critical at all stages in the care of patients with head injury. Early tracheal intubation may be lifesaving in patients with partial airway obstruction and CO_2 retention. Injury to the cervical spinal column should be ruled out before any manipulations of the neck are undertaken, unless this delay will compromise the patient's condition (for example, severe airway obstruction). With the airway protected, ventilation controlled, and the initial neurologic evaluation completed, sedation may be advantageous in managing an uncooperative or combative patient with a closed-head injury.

Monitoring eye signs is important throughout the perioperative course, including during any required general anesthesia. It is possible for epidural or subdural (or both) hematomas to accumulate while patients are anesthetized for abdominal surgery, orthopedic surgery, or other therapeutic or diagnostic procedures. Routine monitoring of eye signs by the anesthesiologist can lead to early recognition of these lesions, permitting prompt surgical intervention and improved prognosis for the patient.

Concomitant neurologic and nonneurologic injuries requiring surgical intervention necessitate establishment of priorities by the medical team. In some instances, neurosurgeons and general or orthopedic surgeons can work simultaneously, although this necessitates careful planning for appropriate remote positioning of anesthesia personnel and equipment. In most instances when intraabdominal bleeding coexists with an intracranial hematoma, abdominal exploration proceeds first, because decompression of an intracranial hematoma may not improve the patient's condition significantly in the presence of hypotension and decreased cerebral perfusion.

Fluid management in patients with multiple traumatic injuries may be difficult. The large volumes of crystalloids frequently used in patients with abdominal trauma can contribute to cerebral edema in a patient with accompanying head trauma. A solution of 5% dextrose in water without saline is contraindicated in patients with head trauma, for the reasons outlined previously. Monitoring of cardiac filling pressures and selection of replacement fluids with the least tendency to aggravate cerebral edema are helpful from the neurologic standpoint. Therapeutic steps such as anticoagulation, which might be of benefit in some patients (for example, traction after othopedic injuries), may be contraindicated in the early therapy of a patient with head injury.

Certain precautions should be recognized before regional anesthesia is used for nonneurosurgical procedures in patients with head trauma. Spinal or epidural anesthesia might increase the risk of neurologic damage by causing sudden changes in CSF pressure (206). A sudden decrease in spinal CSF pressure could precipitate uncal or cerebellar herniation. An increase in pressure in the epidural space also could be detrimental. Peripheral nerve or plexus blocks can be used in these patients, although surgery under regional anesthesia in a confused or combative patient can be difficult. Judicious sedation in conjunction with a regional anesthetic technique may work well, if hypoventilation or airway difficulties (or both) are avoided.

When indicated, general anesthesia utilizing appropriate agents and techniques based on their effects on cerebral metabolic rate, CBF, intracranial blood volume, CSF dynamics, and ICP can make this a safe technique. Barbiturates and opiates frequently are employed because of their effects on CMR, CBF, and ICP. From a neurologic viewpoint, the use of ketamine should be avoided. As noted earlier, the use of inhalation agents in patients with increased ICP has been controversial, particularly with regard to the use of halothane. Clinical studies indicate that halothane can be used safely in patients with increased ICP if hypocapnia is induced before the halothane is introduced (138). Recent reports (139,181) suggest that, from a neurologic point of view, isoflurane may be preferable when a volatile agent is indicated.

The patient with a closed-head or cervical spinal column injury and a full stomach presents problems regarding tracheal intubation. Awake intubation or fiberoptic intubation with appropriate sedation may be useful in a cooperative patient but can be difficult in an uncooperative patient. In addition, coughing, straining, or bucking can increase ICP. If a rapid induction and intubation technique is required, appropriate steps including preoxygenation, head-up tilt, cricoid pressure, and rapid intravenous administration of thiopental and succinylcholine, with a large-bore suction immediately available, should be included. Recognizing that the use of succinylcholine in a patient with increased intracranial pressure is controversial, we nevertheless have used succinylcholine in patients with intracranial mass lesions, when indicated and with appropriate precautions. We also have used pancuronium or metocurine to facilitate intubation in patients with intracranial mass lesions in whom succinylcholine was relatively contraindicated (see the muscle relaxants section above). It is anticipated, and early experience confirms, that atracurium and vecuronium will offer definite advantages in these patients.

Monitoring is critical. In addition to the standard esophageal stethoscope, electrocardiogram, temperature probe, and blood pressure cuff, monitoring of direct arterial pressure, end-tidal CO_2, and pulmonary artery pressure when indicated may be extremely helpful in patients in whom systemic pressure is unstable and control of $Pa{CO_2}$ is critical. Excessive surgical delays due to placement of arterial or pulmonary artery cannulas are not advisable, however, because they can increase morbidity secondary to a developing intracranial pathology. When a cannula has not been inserted before the patient's arrival in the operating room, the anesthesiologist must decide whether direct hemodynamic pressure monitoring during induction is more important than initially establishing increased $Pa{O_2}$, cerebral metabolic depression, airway control, and hypocapnia in that patient. When relative priorities indicate, arterial and other cannulas can be inserted during or after induction of anesthesia and tracheal intubation. The importance of monitoring pupillary signs already has been stressed.

As with neurosurgical patients, patients undergoing other types of surgery with accompanying closed-head injuries should be evaluated neurologically before leaving the operating room at the end of a procedure. Localizing or worsening neurologic signs may necessitate further neurologic diagnostic procedures at this time. Choice of an anesthetic technique that permits the prompt emergence from anesthesia facilitates this neurologic examination immediately after surgery. If response to command cannot be elicited, a patient's response to painful stimuli should be intact and demonstrate bilateral extremity movement compatible with the preoperative neurologic examination. Early extubation of the responsive awake patient can decrease the risk of increased ICP secondary to postoperative coughing. Most patients with closed-head trauma that is producing delirium or coma will need airway support until neurologic improvement ensues, however.

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1985;64:175–8

Clinical Report

Subdural Migration of an Epidural Catheter

Craig T. Hartrick, MD, Charles E. Pither, MD, Umeshraya Pai, MD, P. Prithvi Raj, MD, and Thomas A. Tomsick, MD

Catheter techniques for providing continuous epidural analgesia have enjoyed widespread use. Properly placed and properly managed, epidural catheters can be left in place for prolonged periods. Catheters initially placed within the epidural space have, however, been reported to migrate subsequently to intravascular or subarachnoid positions (1,2). In addition, "massive extradural spread" (as distinguished from subarachnoid injection) that sometimes follows the introduction of small amounts of local anesthetic during attempted epidural anesthesia has been attributed to subdural injection (3). Although initial placement of epidural catheters into the subdural space has been documented radiographically (4,5), to our knowledge, no case of delayed migration into a subdural position has been reported. The following is a case report describing subdural migration of an epidural catheter after four days in the epidural space.

Case Report

A 54-yr-old, 50-kg woman with a 15-yr history of post-traumatic back, hip, and knee pain resulting from multiple fractures was admitted to the pain service. She had previously undergone total knee and total hip replacements, but continued to experience extensive myofascial pain with significant functional limitation. Having failed to respond to therapeutic injections of myoneural trigger points in concert with outpatient physical therapy, the patient was admitted for continuous epidural analgesia and intensive physical therapy.

An epidural catheter was inserted at the L3–4 interspace using a midline approach with a 17-gauge Tuohy needle. A Curity catheter was inserted without difficulty 3 cm into the epidural space. After a 2-ml test dose of 2% lidocaine, 20 ml of 3% 2-chloroprocaine was administered in increments and retrograde differential studies performed. The upper extent of anesthesia as determined by pinprick was T5. The patient tolerated the procedure well, and after complete regression of sensory blockade, 3 ml of 2% lidocaine followed by 15 ml of 0.5% bupivacaine in 5-ml increments was administered. Anesthesia was thereafter maintained with a continuous infusion of bupivacaine, 0.25%, at a rate of 10 ml/hr. This resulted in a band of sensory analgesia, as determined by pinprick, from T12 through L4 on the right and T12 through L5 on the left. Due to excessive motor blockade on the second day, the infusion was changed to bupivacaine, 0.1%, at 15 ml/hr with 9 mg/hr of meperidine. This resulted in excellent analgesia, reduced sensation to pinprick in the lumbar dermatomes bilaterally, and return of full motor function.

The morning of the fourth day of infusion, the patient had her usual physical therapy exercises. Approximately 30–45 min later, while sitting in bed, she noticed a rapidly ascending level of anesthesia that soon produced tingling fingers. Systolic blood pressure was 70 mm Hg and she complained of nausea. The epidural infusion was immediately discontinued and the hypotension corrected with intravenous fluid administration. Sensory examination revealed hypoesthesia from C6 through S5 bilaterally, without significant loss of somatic motor function. Initially, it was felt the catheter might have migrated into the subarachnoid space, despite the absence of motor weakness. However, no CSF could be aspirated

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Address correspondence to Dr. Raj, Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0531.

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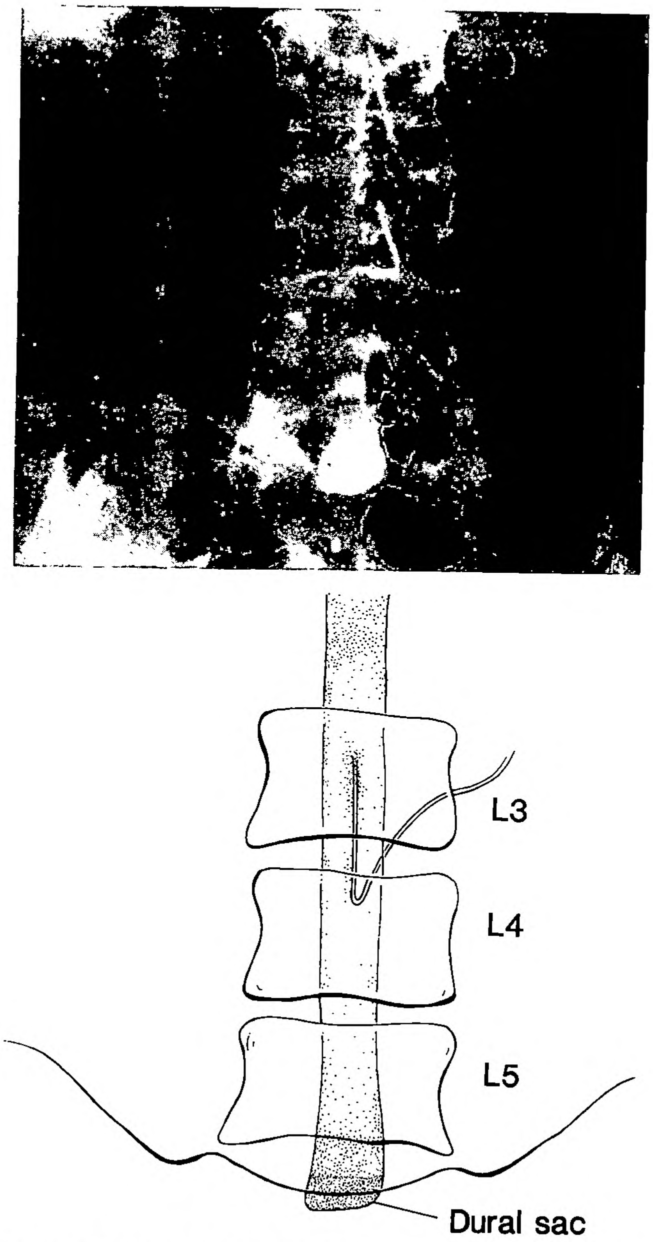

Figure 1. AP view. Contrast medium introduced through the catheter in supine position outlines the lower extent of the dural sac.

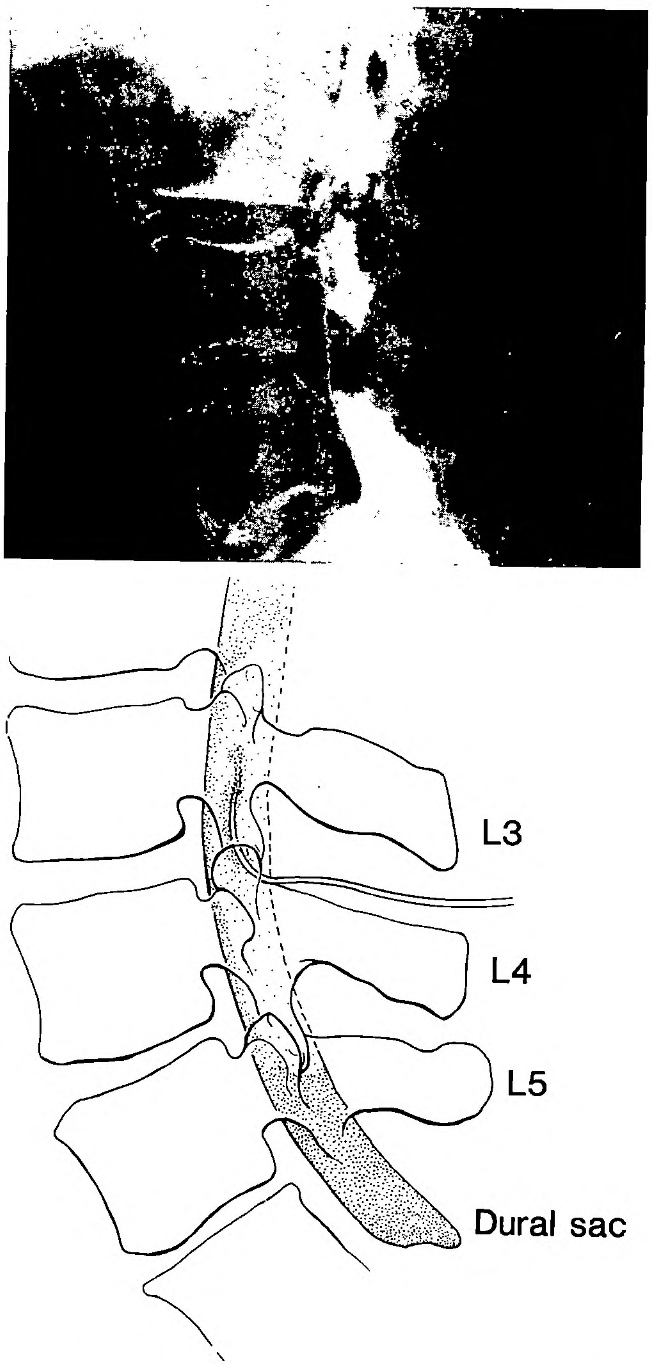

Figure 2. Lateral view. Contrast fails to outline nerve roots. The posterior extent of the subdural space is not well seen as the thin layer of dye is easily obscured by the superimposed facet regions.

through the catheter. The position of the catheter was examined radiographically. Eight ml of metrizamide was injected through the catheter. Radiographic findings indicated that the majority of contrast entered the subdural space (Figs. 1,2), although it is impossible to rule out the presence of some contrast in the subarachnoid space at the caudal termination of the thecal sac.

At this point in the clinical course, the therapeutic goal had been only partially realized. Withdrawal of the catheter back into the epidural space or reinsertion were considered, but it was felt that leaving the catheter in the subdural space would be both therapeutically effective and safe if the rate of infusion and the concentration of local anesthetic injected were decreased. The infusion was therefore resumed, after a 2 ml bolus of bupivacaine, 0.1%, using 3 ml/hr of

0.05% bupivacaine. This produced no evidence that sensory block was obtained. On the next day, therefore, a 2-ml bolus of bupivacaine, 0.5%, was administered over 5 min; this resulted in loss of pinprick sensation from T10 through L3 on the right and from T8 through L4 on the left without motor weakness. The previous infusion was continued, however, but by the next morning, there was again no detectable sensory level. At this time, another 2-ml bolus bupivacaine, 0.5%, was administered, which again resulted in a band of hypoesthesia from T9 through L4 on the right and T9 through L5 on the left. All bolus injections were carried out in a 45° head-up semirecumbent position. The infusion was discontinued the next day and the catheter removed. The skin fixation was found to be unchanged from the time of insertion and the catheter was complete and undamaged. The patient was discharged with considerable improvement in back and hip mobility without a headache at any time during the treatment.

Discussion

The subdural space is the potential space between the dura and the arachnoid membranes. Solutions introduced into this space can be expected to distribute widely. Unlike the epidural space, which is obliterated above the foramen magnum by the fusion of the dura to the periosteum of the cranium, no such limitation is imposed upon the subdural space. Consequently, local anesthetic injected subdurally can produce a state resembling that of total spinal, hence the misnomer "massive extradural" (3).

Clinically, subdural block can be distinguished from spinal block in that the former generally produces only moderate hypotension, a level of anesthesia with slow onset and relatively rapid recovery, and progressive respiratory depression, as opposed to sudden apnea (3,6). Even when small amounts of local anesthetics are injected, the drug is spread over a wide area. This extensive spread results in a weak and sometimes patchy anesthesia (5). Radiographically, the appearance of the subdural space after injection of contrast media has been well described because this space is not uncommonly entered during attempted myelography (7). The deliberate injection of small amounts of neurolytic agents into the subdural space under fluoroscopic control has been described as an effective method for control of cancer pain (8).

In the case presented, the clinical course was consistent with a catheter placed within the epidural space with subsequent migration, perhaps during vigorous exercise, into a subdural space. The onset of anesthesia was gradual, perhaps over 30–45 min which is consistent with previously described subdural injections. The lack of significant motor block is also consistent with subdural injection. The infusion of bupivacaine at 1.5 mg/hr, over presumably less than one hour, represented, nevertheless, a mass of drug sufficient to ascend as high as C6, as determined by

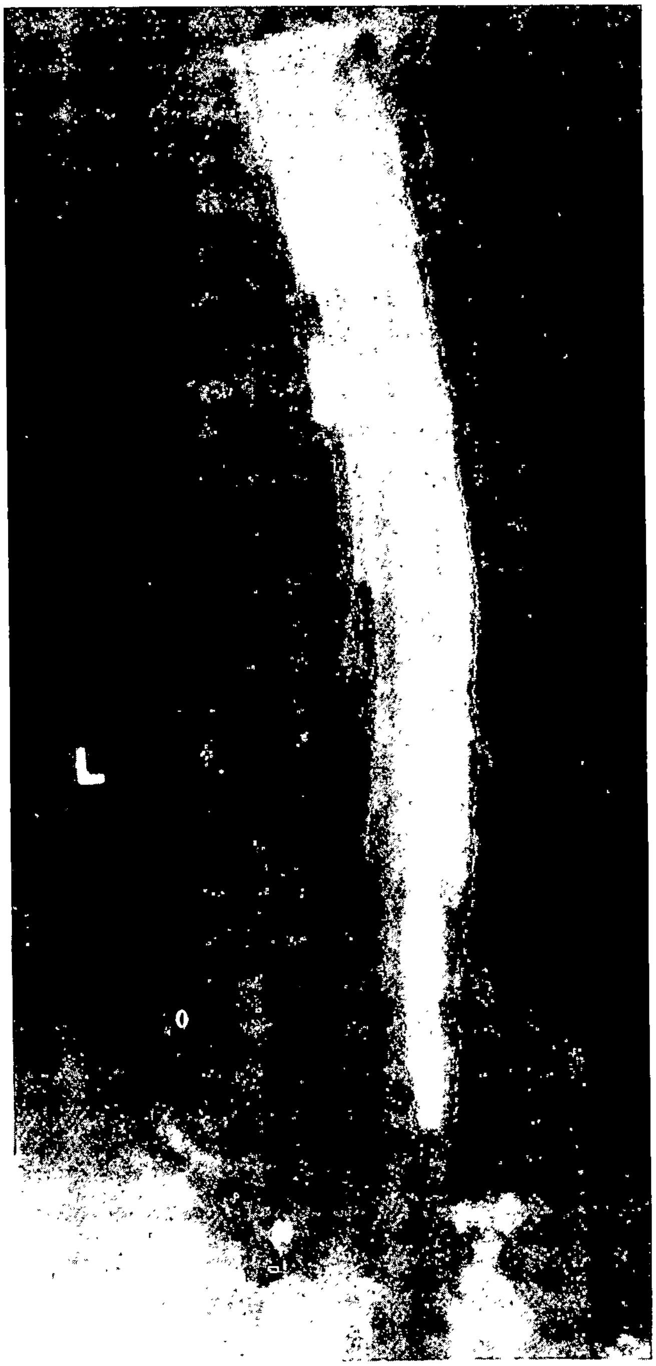

Figure 3. Normal lumbar myelogram (subarachnoid injection) for comparison. The pointed lower end of the subarachnoid space is well identified. Nerve roots and cauda equina are clearly outlined.

hypoesthesia to pinprick. Dispersion of this amount of drug over such a wide region would be expected to lack sufficient density to induce motor blockade.

The radiologic findings after metrizamide injection were highly suggestive of the presence of the contrast material in the subdural space. An epidural injection would be free to spread into the caudal canal. Radiologic visualization of dye above the level of the caudal canal is, however, difficult in the AP view, as the subdural space is so narrow that only a very thin film of contrast material is present. The lateral view better demonstrates the extent of spread (Figs. 2(A), (B)), but fails to outline nerve roots or cord as would be expected on subarachnoid injection (Fig. 3).

Further clinical confirmation of placement of the tip of the catheter in the subdural space was obtained after the subsequent bolus injections. Segmental subarachnoid anesthesia can, of course, also occur, as in this case, when the tip of a catheter lies in subarachnoid space (9,10). However, a bolus injection of 10 mg of bupivacaine in 2 ml, if introduced slowly into the lumbar subarachnoid space, would have been expected to induce a low spinal block that extended to include all sacral roots, sensory as well as motor (11). However, on both occasions, a band of segmental analgesia, sparing the sacral roots, was produced, without motor block. Additionally, the small amounts of local anesthetic that were injected after migration of the tip of the catheter would have been, in our experience, sufficient to maintain subarachnoid block; however, this mass of drug was inadequate, when injected into the subdural space, to maintain any demonstrable sensory blockade by pinprick examination.

While epidural catheters can be safely used for prolonged periods, migration into subarachnoid, intravascular, or subdural positions can occur. The subarachnoid and subdural migrations can be distinguished on clinical and radiologic grounds. Migration of well placed epidural catheters is quite uncommon, but the incidence may increase as epidural catheters are left in situ for longer periods of time in physically active patients. Nevertheless, if continuous infusions of drugs into epidural catheters are to be safely administered, maintenance of the correct position of the tip of the catheter must be assured by frequent measurements of the levels of anesthesia achieved.

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Letters to the Editor

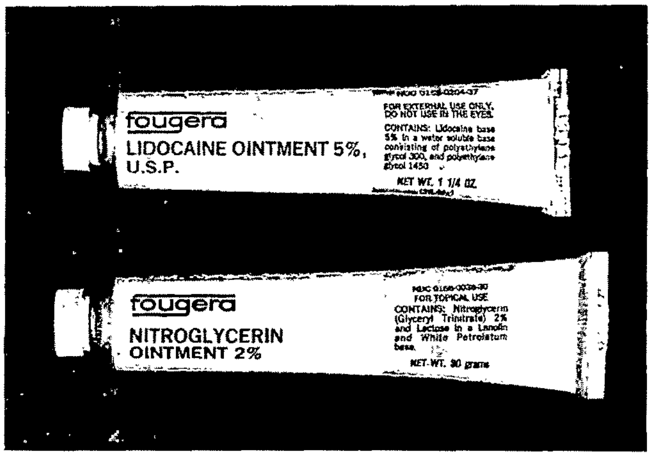
Be Aware and Read

To the Editor:

Many times we take for granted in our practice as anesthesiologists the color of drug vials or ointments without actually reading the labels. In our department we lubricate our endotracheal tubes with lidocaine ointment 5% (E. Fougera and Company, Division of Byk-Gulden, Inc.). The same manufacturer makes a nitroglycerin ointment 2%. Both tubes have a yellow stripe around them (Fig. 1). Both shades of yellow are very similar. The nitroglycerin ointment 2% found its way into our anesthesia equipment drawer and was applied to an endotracheal tube as lubrication. The endotracheal tube was not inserted because it was noted that the ointment was more yellowish in color. Then looking more carefully it was noted to be nitroglycerin ointment 2%. We must never relax our vigil. Be aware and read all labels.

Murray A. Kalish, MD
Department of Anesthesiology
University of Maryland Hospital
22 South Greene Street
Baltimore, MD 21201

Figure 1. *Above:* lidocaine ointment 5%; *below:* nitroglycerin ointment 2%.


fougera
LIDOCAINE OINTMENT 5%, U.S.P.
FOR EXTERNAL USE ONLY. DO NOT USE IN THE EYES.
CONTAINS: Lidocaine base 5% in a water soluble base consisting of polyethylene glycol 300, and polyethylene glycol 1450
NET WT. 1 1/4 OZ.
fougera
NITROGLYCERIN OINTMENT 2%
FOR TOPICAL USE
CONTAINS: Nitroglycerin (Glyceryl Trinitrate) 2% and Lactose in a Lanolin and White Petrolatum base.
NET WT. 30 grams

Skin Blood Flow Measured by Thermal Clearance Method in Anesthesia

To the Editor:

General anesthesia is associated with circulatory changes (1), the complexities of which are so great they are often difficult to measure noninvasively under clinical conditions. We have recently used the noninvasive techniques for measurement of thermal clearance described by Roussel et al. (2) as a means for evaluating microcirculation responses to general anesthesia under clinical conditions. While not necessarily applicable to other circulatory beds, the results shed light on one aspect of thermoregulation during anesthesia and may be helpful in establishing more generalized concepts and principles regarding the effects of anesthesia on the microcirculation.

The thermal clearance technique described by Roussel et al. is based on measurement of thermal conductivity using a probe applied to the skin. The probe includes a disc 20-mm in diameter and 4-mm thick, in the center of which is a heating device (Fig. 1). The skin temperature gradient between the center and the periphery of the probe is measured from twelve thermocouples (Cu–Ce) in series. Six hot junctions are located in the center and six cold junctions in the periphery. The mean skin temperature of the periphery is calculated with allowance for discarding variations due to direction of blood flow. Therefore, the probe is hardly affected by the presence of a large vessel or undirectional blood flow. The proportional, derivative, and integrative actions of this automated device maintain a constant temperature gradient of 2°C between the center and the periphery of the probe (with an accuracy of 3×10^{-3} °C). The electrical power necessary to maintain the constant temperature gradient is dependent on the skin blood flow. The heat produced in the center of the probe is removed by the flow of blood. The decrease in temperature, therefore, represents blood flow.

An example of the use of this probe is as follows: A 27-yr-old man, without a history of cardiovascular disease, was scheduled for internal saphenous vein stripping. Premedication given 1 hr before surgery consisted of 1 mg flunitrazepam, 25 mg alimemazine, and 0.5 mg atropine intramuscularly. After baseline measurements were made, 5 mg

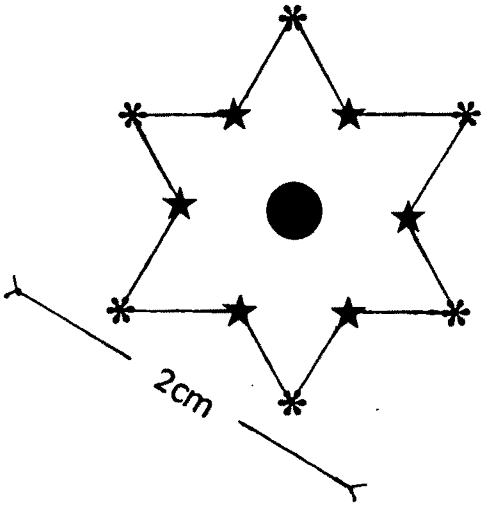


Figure 1. The probe, which allows measurement of thermal conductivity, includes a disk applied to the skin. Its schematized surface is shown. Symbols: ●, heating center; ★, hot thermocouple (Cu–Ct); *, cold thermocouple (Cu–Ct).

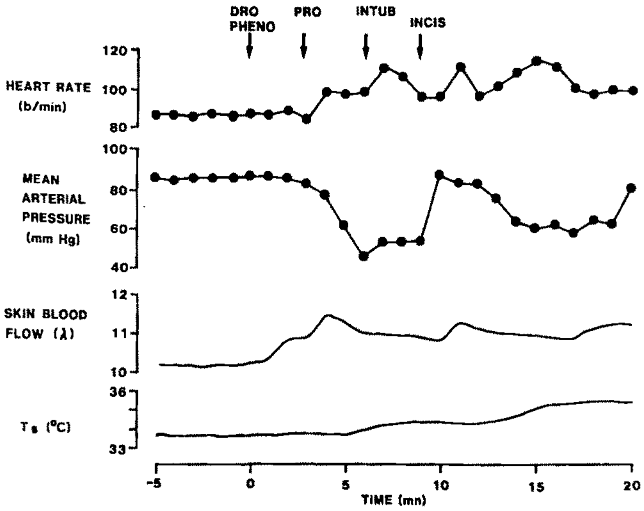


Figure 2. Four parameters were simultaneously registered for 25 min, before, during, and after induction of general anesthesia. Abbreviations: DRO, droperidol intravenous bolus; PHENO, phenoperidine intravenous bolus; PRO, propanidid infusion; INTUB, tracheal intubation; INCIS, skin incision; T_s, skin temperature; λ, the expression of thermal conductivity (1×10^{-4} cal/cm °C·sec).

droperidol and 1 mg phenoperidine were given intravenously at time zero (Fig. 2). Three minutes later anesthesia was induced by the intravenous infusion of propanidid. Six minutes after the droperidol and phenoperidine were given, 10 mg alcuronium was given and orotracheal intubation was performed. Heart rate, mean arterial pressure, skin blood flow, and skin temperature were measured at 1 min intervals.

As shown in Figure 2, skin blood flow changed before heart rate, mean arterial pressure, or skin temperature did. One minute after droperidol and phenoperidine, skin blood flow had increased about 10%. It increased another 10% after intubation of anesthesia with propanidid, at which time the heart rate started to increase. Hypotension (a 30% decrease in mean arterial pressure) was not associated with a decrease in cutaneous blood flow. Skin temperature, the least reliable index of cardiovascular changes, increased not only slowly, but also slightly.

Measurement of skin blood flow by thermal clearance is a reliable, noninvasive, and sensitive technique with considerable potential as a method for monitoring of the microcirculation and quantification of the pharmacologic effects of anesthetics on this circulation under clinical conditions.

Christian-Serge Degoute, MD
Jean-Louis Saumet, MD
Vincent Banssillon, MD
Service d'Anesthésie-Réanimation
Service d'Exploration Fonctionnelle Vasculaire
Centre Hospitalier Lyon-Sud, 69310—Pierre-Benite, France

Alain Dittmar, PhD
Laboratoire LA 181, CNRS, Faculté de Médecine
8, avenue Rockefeller, 69008—Lyon, France

Clearance from Cerebrospinal Fluid of Intrathecally Administered β-Endorphin in Monkeys

To the Editor:

We read with interest the article by Lee et al. (1) regarding the clearance from cerebrospinal fluid of intrathecally administered β-endorphin in monkeys. However, we question their conclusion that β-endorphin is eliminated from spinal fluid by bulk diffusion similar to inulin based on the unity of clearance ratio.

The rate of elimination of a drug after an intravenous bolus administration can be described by

$$-\frac{dA}{dt} = Cl \cdot C \tag{1}$$

where A is the amount of the drug in the body, Cl is the total body clearance of the drug, and C is the concentration of the drug in the plasma.

Integrating equation (1):

$$-\int_0^\infty dA = \int_0^\infty Cl \cdot C \cdot dt \tag{2}$$

$$A_0 - A_\infty = \int_0^\infty Cl \cdot C \cdot dt \tag{3}$$

where A_0 is the amount of the drug in the body at zero time, and A_∞ is the amount of the drug at infinite time after administration.

Because at infinite time all the drug will be eliminated from the body, A_∞ equals zero. After an intravenous bolus administration, the amount of the drug at zero time should represent the dose D. Assuming first order elimination of the drug, i.e., clearance is a constant, equation (3) then becomes:

$$D = Cl \cdot \int_0^\infty C \cdot dt \tag{4}$$

For drugs A and B, respectively,

$$D_A = Cl_A \cdot \int_0^\infty C_A \cdot dt \tag{5}$$

$$D_B = Cl_B \cdot \int_0^\infty C_B \cdot dt \tag{6}$$

Making the following assumptions: intravenous bolus administration, first order elimination, and the doses for drugs A and B are the same, equations (5) and (6) then equal:

$$D_A = D_B = Cl_A \cdot \int_0^\infty C_A \cdot dt = Cl_B \cdot \int_0^\infty C_B \cdot dt \tag{7}$$

That is,

$$\frac{Cl_A}{Cl_B} = \frac{\int_0^\infty C_B \cdot dt}{\int_0^\infty C_A \cdot dt} = \frac{\mathrm{AUC}_B}{\mathrm{AUC}_A} \tag{8}$$

where AUC_A is the area under the plasma concentration vs time curve of drug A, and AUC_B is the area under the plasma concentration vs time curve of drug B.

Equation (8) is the clearance ratio stated in the article. Even though the authors administered the drugs intrathecally and determined the concentration of drugs in the spinal fluid, one simply needs to substitute the spinal fluid concentration of the drugs for the drug concentrations in the plasma in equation (8). The authors found the clearance ratio to be close to unity and suggested that β-endorphin is cleared from spinal fluid similar to that of inulin, i.e., by bulk absorption.

However, without knowing the specific activity of [^{14}C]-inulin, one does not know whether the dosages of [^{14}C]-inulin and β-endorphin were the same. Even if this assumption holds, the fact that the clearance ratio of two drugs equals unity means that these two drugs are cleared in the body by the first order process and does not necessarily mean that they are cleared by the same mechanism, e.g., passive diffusion, filtration through a pore, or enzymatic degradation. Both drugs can be eliminated by the first order process. However, one drug can be eliminated by passive diffusion, whereas the other drug can be eliminated by enzymatic degradation at low dose range.

In summary, in our opinion, the suggestion from the authors that β-endorphin is eliminated from spinal fluid by bulk absorption similar to inulin appears to be questionable.

Sheng K. Lin, PhD, MD
Kevin K. Tremper, PhD, MD
Department of Anesthesiology
University of California, Irvine Medical Center
101 City Drive South #81A
Orange, CA 92668

Reference

1. Lee VC, Burns RC, Dubois M, Cohen MR. Clearance from cerebrospinal fluid of intrathecally administered β-endorphin in monkeys. Anesth Analg 1984;63:511–4.

In Response:

We appreciate the comments by Drs. Lin and Tremper.

Our method of deriving clearance ratio from the areas under the respective curves of elimination is utilized in studies of elimination of drugs from the plasma compartment. We feel that this technique is applicable to elimination of drugs from the cerebrospinal fluid (CSF) compartment as well.

The elimination of inulin is recognized to be a first order process because it is eliminated passively by bulk absorption of CSF, which is dependent only on hydrostatic pressure and rate of CSF formation (1). It is not known whether the elimination of β-endorphin is strictly first order, though this is suggested by the parallel slopes of the respective elimination curves in our study.

When calculating ratio of clearance of two substances by determining respective areas under the curves of elimination as we have done, it is true that the doses of the two species should be numerically equal, as Lin and Tremper point out. However, this mathematical relationship also remains true if the amounts of each drug injected are standardized as one unit dose and respective concentrations are expressed as fraction of unit dose per volume of plasma or CSF sampled. Our data analysis is based on this.

Our data show that the rate, but not necessarily the mechanism, of elimination of β-endorphin from the CSF is similar to that of inulin. The latter substance is eliminated solely by bulk absorption of CSF, which is passive filtration of spinal fluid through the sieve-like processes of the arachnoid villi (1). Indeed, the clearance rate of inulin from CSF is a direct measure of the rate of bulk absorption of CSF much in the same way that clearance rate of inulin from plasma is a direct measure of glomerular filtration. If one postulates a critical pore size for this, it is conceivable that a variety of substances is filtered freely by the arachnoid villi, as demonstrated by Welch and Pollay (2). It would seem that β-endorphin (MW 3300) may be of appropriate molecular size for filtration when compared to inulin (MW 5000), although other factors such as molecular structure and charge are also important.

In any case, we feel that comparison of the rate of clearance of an intrathecally administered substance such as β-endorphin to that of inulin is a pharmacologically useful measurement. This technique permits us to conclude that the elimination of β-endorphin from CSF appears to be relatively prolonged and at least as slow as the elimination of inulin. As we stated in our article, this may explain the observation that intrathecally administered β-endorphin seems to have a longer duration of action than that of intrathecal morphine (3).

Victor C. Lee, MD
Michel Dubois, MD
Georgetown University Hospital
3800 Reservoir Rd., NW
Washington, DC 20007

Richard S. Burns, MD
National Institute of Mental Health
9000 Rockville Pike
Bethesda, MD 20205

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Psychomotor Tests and "Street Fitness"

To the Editor:

We enjoyed reading the article by Denis et al. (1), but would like to offer a few comments. The authors used enflurane or isoflurane for 25–150 min, but there is no mention of the duration of effect of these two different anesthetics used on the psychomotor tests.

The study demonstrated a high percentage of errors in patients tested at 1.5 hr on the track tracer. Experience in ambulatory surgical centers indicates that many patients having 25–30 min anesthetics are discharged "street fit" in one hour, at a time when, according to this study, they may have had abnormal results by psychomotor testing.

Patients undergoing surgery on eyes, arms, or dominant hands were excluded from this study because of these patients' inability to take these tests. This limits the administration of these tests, if they are necessary at all, in most ambulatory surgery, in which a significant number of patients undergo eye or arm surgery. Results obtained from these psychomotor tests vary with each individual patients, because recovery from anesthesia varies from patient to patient, and thus results obtained from other patients cannot be extrapolated to patients who cannot take these tests.

The track tracer test, compared to polar pursuit and pegboard tests, was proved to be reliable, but the validity of the track tracer test as a test for "street fitness" is questionable. The authors state that the track tracer test determines return to preoperative baseline performance during "temporary arousal" during recovery, but that it "depends on fine motor control" and may not accurately reflect "disturbed higher motor functions." This indicates poor correlation of the test to "street fitness," which the authors acknowledge. Yet, in the next sentence they state that the test is an adequate measure of recovery from anesthesia.

Finally, we were surprised when they suggested using the track tracer test for medicolegal purposes! No one wants to take a permanent record of this test to the court of law in the belief that results of this test would defend anesthesiologists when the correlation of this test to "street fitness" has not been confirmed.

These psychomotor tests have been effectively used to compare the effect of drugs on the brain objectively, but do clinical anesthesiologists really need a psychomotor test to decide street fitness?

Patrick Healy, MD
Tadikonda L.K. Rao, MD
*Loyola University Stritch
School of Medicine
2160 South First Avenue
Maywood, IL 60153*

Reference

1. Denis R, Letouneau JE, Londorf D. Reliability and validity of psychomotor tests as measures of recovery from isoflurane or enflurane anesthesia in a day-care surgery unit. Anesth Analg 1984;63:653–6.

In Response:

The comments made by Doctors Healy and Rao refer mainly to "street fitness," a criterion that was not used in our study. They also compared this study to their clinical experience, the parameters (sample, type of surgery, length of anesthesia, etc.) of which may significantly differ from those we indicated. The confusion of "street fitness" with the parameters used in our study leads them to a discussion of the internal validity of the study (flaws in the study) instead of its external validity (the degree to which the results may be generalized).

Moreover, when comparing the results of our study with "street fitness" they should bear in mind the fact that the vertical bars in Figure 3 represent roughly two-thirds of the cases in the sample (±1 SD). One-third of the cases (i.e., the extreme values) are not represented on the graph, which illustrates the standard deviation rather than the range (see Fig. 3); the cases they mention are probably those with a short anesthesia period (less than the average of 50 min) corresponding to the (quote) "patients having 25–30 min anesthetics discharged street fit in one hour."

The fact that the test was not used with patients who had surgery of the eye or the dominant arm refers to the external validity of the study and is probably of minor importance because the test should be used within a battery. It was not our intent to suggest that one test alone be used for medicolegal purposes! Furthermore, any research on a test should be replicated many times by different investigators and norms established before it can be used for this purpose. As indicated in the paper, "the correlation between the results on the track tracer and 'street fitness' should be measured" before it is used for clinical purposes.

The fundamental issue with the use of psychomotor tests in the evaluation of recovery from anesthesia probably lies in the fact that it is difficult to distinguish between residual motor paralysis and the residual effect of the anesthetic agents (enflurane or isoflurane) used. The issue of "temporary arousal" during testing cannot easily be solved because it is difficult to know if the sample of the performance during testing is representative of the condition of the patient.

R. Denis, MD
J. Letourneau, PhD
*University of Montreal
Montreal, Quebec, Canada*

D. Londorf, MD
*McGill University
Montreal, Quebec, Canada*

Book Review

Computing in Anesthesia and Intensive Care

Omar Prakash, ed. Boston: Martinus Nijhoff, 1983.

Computing in Anesthesia and Intensive Care, edited by Omar Prakash of Erasmus University, Rotterdam, is a collection of papers from the Second International Symposium on this topic, held in Rotterdam on September 6–10, 1983. As is typical for this type of volume, the contributions cover a variety of topics at a variety of levels from different points of view. The book is noteworthy in that it appeared very soon after the symposium.

The 33 contributions cover a wide range of computer applications, ranging from relatively well-established areas such as drug dosage calculations to developing areas such as automatic control of anesthesia delivery and nuclear magnetic resonance. The editors provide no categorization of papers, and as a result, the book is somewhat difficult to use. It would have been a great help if the keynote speakers and the major tutorials had been identified and if the papers had been grouped or identified in general categories. Even the inclusion of the symposium program would possibly have helped. The reader is left to organize the material for himself.

My classification of topics includes three tutorial articles, six articles related to data management, four on educational applications, five on computer control of anesthesia, three on electrophysiologic monitoring, four that involve numerical analysis or calculations, six on a variety of monitoring applications, and a few miscellaneous articles. Some of the papers describe original research, some present tutorial material on specific techniques, and a few describe experiences with commercial equipment. The authors generally assume the reader is familiar with computers, but not an expert. However, even the papers presenting original research do not present much detail. A neophyte reader would need to refer extensively to the references given.

Because the pages were photo-offset from manuscripts submitted by the authors, there is no uniformity of type, page layout, or format for figures and references. However, the production quality of the book is excellent, and the text and figures are generally easy to read. The use of word processors for preparation of many of the original manuscripts, as would be expected from computer-oriented researchers, had a significant positive impact on readability. There were a number of typographical errors, but fewer than might be expected in view of the speed of preparation of the book.

This book is probably most appropriate for a reader seeking a general idea of the types of computer applications currently being investigated in anesthesia and intensive care. The editors, publisher, and authors are to be commended for providing the volume so quickly. Although the coverage is not comprehensive, most of the areas currently being investigated are represented. As with most proceedings, the quality varies considerably among the papers. The book is not sufficiently detailed for an investigator who is seriously considering becoming involved in a particular area, but it does provide a useful snapshot of where these kinds of applications stand today.

J. Robert Boston, PhD
Department of Anesthesiology
University of Pittsburgh School of Medicine
Pittsburgh, PA 15261

59th CONGRESS
T. H. SELDON DISTINGUISHED LECTURE

Standards for Excellence

To be presented Monday, March 11, 1985 by

M. T. Jenkins, MD

McDermott Professor of Anesthesiology
University of Texas Southwestern
Medical School
Dallas, Texas

"Pepper" Jenkins—distinguished anesthesiologist, gentleman, scholar, and raconteur—will address our meeting on a topic that he certainly exemplifies. The IARS is honored to have him grace our podium as he has the specialty for so many years.

T. H. Seldon, MD, FFARCS(I)

Rochester Minnesota/Sun City Arizona

The 1985 T. H. Seldon Distinguished Lecture is the third to be sponsored by the International Anesthesia Research Society to honor Dr. T. "Harry" Seldon for his distinguished service to the Society and to the specialty as Editor of *Anesthesia and Analgesia* for 23 years before his retirement in 1977.

Anesthesia and Analgesia

Abstracts Presented at the International Anesthesia Research Society 59th Congress

Houston, Texas
March 9–13, 1985

Journal of the International Anesthesia Research Society

Title: **MIDAZOLAM PHARMACODYNAMICS AND PHARMACOKINETICS IN DOGS DURING ACUTE HYPOVOLEMIA**

Authors: P Adams, M.B., S Gelman, M.D.,Ph.D., JG Reves, M.D., DJ Greenblatt+, M.D., JM Alvis, M.S., E Bradley, Ph.D.*
Affiliation: Departments of Anesthesiology, and Biostatistics and Biomathematics*, University of Alabama in Birmingham, Birmingham, Alabama, 35294, Division of Clinical Pharmacology+, New England Medical Center, Boston, Massachusetts 02111

Introduction: There are data suggesting that midazolam increases venous capacitance with subsequent compensatory mobilization of splanchnic blood volume into the systemic circulation.(1) These data might mean that in hypovolemic states midazolam induced venodilation would not be accompanied with a compensatory blood volume mobilization, resulting in reduced cardiac output (CO) and hypotension. This study was designed to test the hypothesis that acute hypovolemia would compromise the compensatory hemodynamic mechanisms to midazolam and prolong its clearance and action.

Methods: Experiments were performed on 8 female beagle dogs. Four days prior to the experiment, a pediatric Swan-Ganz catheter was inserted into the pulmonary artery and another catheter was introduced into the right femoral artery. The external ends of the catheters were brought out through the back of the neck by subcutaneous tunnel. Dogs were allowed to recover. Each dog received two doses of midazolam, 10 mg/kg, four days apart during normovolemic (N) and hypovolemic (H) states in a random order. Hypovolemia was achieved by withdrawal of 1/3 of calculated blood volume (26 ml/kg). Midazolam concentrations were determined by electron capture gas liquid chromatography in blood samples taken at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hrs post-midazolam injection. Midazolam protein binding was determined by equilibrium dialysis using C-14 labeled midazolam.

Results: Midazolam, 10 mg/kg, did not produce unconsciousness during normovolemia; however, all norvolemic dogs were slightly agitated and unable to walk or stand after midazolam. After phlebotomy all dogs were recumbent and 2 were unconscious. After midazolam administration during hypovolemia, four dogs were asleep (10 to 30 min) and the remaining 4 dogs were asleep briefly (5 to 10 min). Hemodynamic results are presented in Table 1. Midazolam caused a significant decrease in systolic blood pressure (SBP) and an increase in heart rate (HR) during N and produced significant decreases in SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) during H. After the administration of midazolam, HR, blood pressure (BP), and CO were significantly lower during hypovolemia than during the normovolemic state; however, there were no significant differences in the percent change in BP and CO between the two states. Elimination half-life (t½β) was significantly longer and total clearance was significantly lower during H than during N. Volume of distribution and protein binding were similar in both N and H states (Table 2).

Discussion: Hypovolemic dogs experienced a more profound hypotension than normovolemic animals. Midazolam appears to produce slightly greater hypotension in the hypovolemic dog (23% decrease in MAP) than reported after diazepam (10%). (2) Pharmacokinetic differences between states N and H for midazolam are probably related to a decrease in hepatic blood flow which always occurs during hypovolemia. (3) Despite the fact that midazolam led to similar decreases in BP and CO percentage wise in states N and H, the absolute values of BP and CO were much lower in the hypovolemic state. These data suggest that midazolam, as many other intravenous agents, (2) can be dangerous for the hypovolemic patient.

References:

1. Gelman S, Reves JG, Harris D. Circulatory responses to midazolam anesthesia: Emphasis on canine splanchnic circulation. Anesth Analg 1983;62:135-139.
2. Priano LL. Renal hemodynamic alterations following administration of thiopental, diazepam, or ketamine to conscious hypovolemic dogs. Adv Shock Res 1983;9:173-188.
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Table 1
Hemodynamics Variables After Midazolam
During Normovolemic and Hypovolemic States

TIME (min)		HR (bpm)	MAP (mmHg)	CO (l/min)	PCWP (mmHg)
0	N	134±20.1	123±17.4	1.09±0.30	6.9±3.1
	H	118±28.3	80±31.5‡	0.48±0.22‡	4.5±0.9*
5	N	161±24.8^{b}	109±22.5^{a}	0.95±0.29	5.7±4.6
	H	108±20.7‡	58±16.7‡^{c}	0.42±0.16‡	3.9±0.6
15	N	148±29.3	107±19.7^{a}	1.02±0.46	6.4±4.7
	H	105±19.2‡	61±17.7‡^{b}	0.49±0.20‡	3.9±0.6*

Values are Mean ± S.D. HR = heart rate, MAP = mean arterial pressure, CO = cardiac output, PCWP = pulmonary capillary wedge pressure. * $p < 0.05$, ± $p < 0.001$ vs normovolemic values at corresponding time; ^{a} $p < 0.05$, ^{b} $p < 0.01$, ^{c} $p < 0.001$ vs values at time zero at corresponding state.

Table 2
Pharmacokinetic Variables of Midazolam
During Normovolemic and Hypovolemic States

	Normovolemic	Hypovolemic
Half-life (t½β hrs)	1.9 ± 0.9	3.2 ± 1.8*
V_1 (l/kg)	1.6 ± 1.5	1.7 ± 1.1
V_d (l/kg)	8.8 ± 4.6	10.9 ± 5.0
Clearance (ml/kg/min)	63.2 ± 17.6	40.8 ± 25.9*
Protein Binding (percent)	95.9 ± 3.2	95.6 ± 2.3

Values are Mean ± S.D. *$p < 0.05$ vs normovolemic state.
V_1 = apparent volume of central compartment, V_d = apparent volume of distribution.

Title: SINGLE TWITCH AND TRAIN-OF-FOUR RESPONSES FOR ATRACURIUM AND VECURONIUM

Authors: H.H. Ali, M.D., S.J. Basta, M.D., J.J. Savarese, M.D., M. Gargarian, M.D., R.F.P. Scott, M.D., N. Sunder, M.D., M. Gionfriddo, B.A.
Affiliation: Anesthesia Laboratories, Department of Anesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA 02114

Introduction: Two common methods of evaluating responses to muscle relaxant administration are evoked single twitch (ST) nerve stimulation and evoked train-of-four (T4) nerve stimulation. ST stimulation at 0.15 Hz has been found to be clinically relevant for determining adequate neuromuscular blockade for tracheal intubation and abdominal surgical relaxation.[1] T4 stimulation (2 Hz for 2 sec once every 10 sec) offers the advantage of following recovery from neuromuscular blockade without the need for establishing a control response.[2,3] Additionally, it has been shown for the older relaxants (d-tubocurarine, metocurine, and pancuronium) that when the ST returns spontaneously to control height, the mean train-of-four ratio is less than 50%.[4] This study was undertaken to define for the new relaxants, atracurium (Atc) and vecuronium (Vec), which method of nerve stimulation is clinically most useful.

Methods: ASA Class I and II patients, age 18-59, were studied. Each patient gave written, institutionally approved informed consent. All were premedicated one hour preoperatively with diazepam 0.15 mg/kg p.o. and morphine 0.1 mg/kg I.M. Anesthesia was induced with fentanyl (6 µg/kg) and thiopental (4-8 mg/kg). The trachea was intubated without a relaxant using topical anesthesia. Ventilation was controlled to maintain end-tidal CO_2 in the range of 35-40 mmHg. Anesthesia was maintained with N_2O/O_2 at a ratio of 4L/2L. After a stable neuromuscular response of 10 minutes, a bolus dose of relaxant was administered and onset time to maximum block and duration to 95% recovery were recorded. The dosage groups were as follows (mg/kg): Atc - 0.06, 0.1, 0.2, 0.4, 0.5; Vecuronium - 0.02, 0.04, 0.06, 0.1. For each drug, approximately half of the subjects were monitored using ST responses at 0.15 Hz and half using T4 responses at 2 Hz for 2 seconds repeated every 10 seconds. These responses were generated by stimulating the ulnar nerve at the wrist using square-wave-supramaximal pulses and monitoring the mechanical response of the adductor pollicis. In the ST groups, when the response had returned to control levels, a T4 was performed and the ratio documented.

Dose response curves were generated for each group using the method of Litchfield and Wilcoxon.[5] Results were analyzed using a student's t-test where appropriate. A $p<0.05$ was considered statistically significant. Values expressed are means ± standard error.

Results: Dose-response curves for ST and T4 stimulation for Atc showed a good fit and parallelism but ED95 values differed significantly. The same was true for Vec. Single twitch ED95 for atracurium was 0.26 mg/kg and 0.20 mg/kg for T4. ST ED95 for Vec was 0.056 mg/kg while for T4 it was 0.037 mg/kg.

The other neuromuscular response data is shown in Table I for Atc and Table II for Vec.

Conclusion: In this study, T4 stimulation is more sensitive in detecting changes in neuromuscular function for both Atc and Vec as shown by lower ED95 values, shorter onsets, and longer durations of action. However, clinically when assessing potency and time to good intubating conditions, ST data yield more useful information. In assessing recovery, when the ST has returned to control, the T4 ratio for both atracurium and vecuronium has recovered more than the classical relaxants. However, for neither drug is the value greater than 75%. Thus for assessing recovery from neuromuscular blockade, T4 nerve stimulation remains superior to ST.

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1. Ali HH, Savarese JJ: Anesthesiology 52:36, 1980.
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3. Lee C: Anesthesia & Analgesia 54:649, 1975.
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Table I
ATRACURIUM

Dose (mg/kg)	Stimu- lation	% Block	Onset (min)	95% Recovery (min)
0.2	ST	73.2±11.1	6.6±0.4	33.5±2.9
	T4	94.1±0.3*	3.9±0.5*	44.1±2.4*
0.4	ST	98.9±0.7	3.9±0.5	51.1±2.7
	T4	99.8±0.1	1.7±0.2*	63.5±2.7*
0.5	ST	100	2.3±0.2	59.1±1.9
	T4	100	1.7±0.1*	67.6±5.4**

*p at least<0.05; ** T4/T1 at 95% ST = 0.69±0.04

Table II
VECURONIUM

Dose (mg/kg)	Stimu- lation	% Block	Onset (min)	95% Recovery (min)
0.04	ST	72.6±14.1	5.3±0.5	26.7±3.7
	T4	97.6±1.4*	3.3±0.6*	31.4±1.8*
0.06	ST	99.1±0.7	4.0±0.5	42.5±3.2
	T4	99.9±0.1	2.7±0.2*	35.7±1.2*
0.10	ST	100	3.8±0.3	48.4±3.7
	T4	100	1.5±0.1*	63.3±7.6**

*p at least < 0.05; ** T4/T1 at 95% ST = 0.60±0.06

Title: DOES SUCCINYLCHOLINE MODIFY THE RESPONSE TO ATRACURIUM?

Authors: H. Ali, M.D., J. Savarese, M.D., S. Basta, M.D., N. Sunder, M.D., M. Gionfriddo, B.A.,
C. Lineberry, Ph.D., A.G. Batson, B.S.
Affiliation: Department of Anesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA
02114, and Medical Department, Burroughs Wellcome Co., Research Triangle Park, NC 27709

Introduction: It has been shown that an intubating dose of succinylcholine (SCh) 1.0 mg/kg potentiates and prolongs the action of pancuronium[1] and d-tubocurarine neuromuscular block and only potentiates atracurium blockade when given 35 minutes after SCh.[2] It is generally acknowledged that SCh is still the relaxant most commonly used for laryngoscopy and tracheal intubation. After recovery from SCh, it is customary to maintain surgical relaxation with a nondepolarizing agent. Atracurium (Atr), an intermediate acting nondepolarizing relaxant has recently become available for clinical use. Its elimination depends on Hofmann reaction and ester hydrolysis. The purpose of this study is to evaluate the effect of SCh 1.0 mg/kg on the response to a subsequent dose of atracurium, depicting a clinically practiced protol.

Methods: Thirty adult ASA I-II surgical patients 19-61 years old were studied after signing an institutionally approved informed consent. Premedication was diazepam 0.15-0.2 mg/kg p.o. and morphine 0.1-0.15 mg/kg I.M. an hour before induction. Control transduced evoked thumb adduction was obtained in response to supramaximal ulnar nerve stimulation at 0.15 Hz via two percutaneous needle electrodes inserted at the wrist under lidocaine skin infiltration. Anesthesia was induced with sodium pentothal 5.0 mg/kg and 60% nitrous oxide in oxygen and ventilation was assisted via a face mask. Patients were divided into two groups. Group A (n=20) was given atracurium 0.3 mg/kg 30 seconds after induction. Group B (n=10) intubation was accomplished in both groups at maximum twitch inhibition and ventilation was controlled with N_2O-O_2 4:2 (L/min). In Group B when the twitch recovered to 5% control height, atracurium 0.3 mg/kg was administered. End tidal CO_2 and temperature were maintained in the normal range. Increments of fentanyl and pentothal were given when clinically indicated. The following measurements were obtained: maximum percent block, onset time, recovery times from injection to 5% and 95% twitch height, and from 5-95% and 25-75% twitch height. Results were compared with student's t-test for unpaired data. Changes were considered significant when $p<0.05$.

Results and Discussion: The onset time to SCH maximum block was 1.04±0.1 min and recovery to 5% twitch height was 8.0±0.9 min. Other data are summarized in Tables 1 and 2.

Table 1

	Max % Block	Onset Time (min)
Atr 0.3 mg/kg (Group A)	98.8±0.3 (92-100)	3.9±0.3 (1.7-6.5)
Atr 0.3 mg/kg after SCh 1.0 mg/kg (Group B)	93.0±2.6 (73-100)	5.3±0.4 (3.2-7.5)
Significance	0.001 P<0.005	0.01 P<0.025

Table 2
Recovery Times (min)

	Injection - 95%	5-95%	25-75%
Group A	48.9±2.5 (33-69.5)	27.1±1.7 (13-43)	11.1±0.8 (6-19)
Group B	32.7±1.4 (26.5-40.7)	21.7±0.5 (20-22.5)	9.3±0.7 (7.5-12.7)
Significance	P<0.001	0.05 P<0.1	0.1 P<0.2

All data are mean±SEM and range.

It appears that an intubating dose of SCh delayed the onset of atracurium peak effect and diminished the magnitude of block. This may be explained by an agonist-antagonist interaction during partial SCh block. While atracurium recovery time from injection to 95% was significantly shortened after SCh, the 5-95% time and the recovery index (25-75%) were not significantly different. Although ester hydrolysis of atracurium is independent of plasmacholinesterase, enzymatic hydrolysis may have been induced by SCh. This may explain the faster recovery in Group B. In conclusion, SCh did not appear to potentiate or prolong atracurium neuromuscular block under this study protocol. The latter may explain the difference in the results when compared with previous studies.

References:

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Title: OMISSION OF SUPPLEMENTARY POTASSIUM PERIOPERATIVELY IN CARDIAC SURGERY

Authors: MW Allard, M.D., and DBC Cheek, M.D.

Affiliation: Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, California 92350

Introduction. Administration of potassium chloride (KCl) has become routine in the perioperative management of cardiac surgery patients. Present literature focuses on the potential dysrhythmic effects of hypokalemia, yet it is admitted that dysrhythmias definitely attributable to hypokalemia have been rare or absent (1). Administration of KCl while on cardiopulmonary bypass (CPB) has been considered safe, but untoward peripheral vascular response can result (2). In this study we report the effects of omitting supplementary potassium in cardiac surgery patients.

Methods. Eighteen patients not on digitalis and/or diuretics undergoing cardiac surgery with CPB were studied, after Human Studies Committee approval and informed consent. Serum K^+ were recorded prior to anesthesia; every 30 minutes on CPB; immediately after CPB; and at six-hour intervals until 24 hours after anesthetic induction. All obligatory K^+ given in perioperative IV solutions, cardioplegia, and bank blood was recorded. Potassium loss was measured and recorded, comprising perioperative urine, operative suction loss, the CPB discard, and postoperative drainage. EKG was recorded throughout the study period with dysrhythmias and EKG signs of hypokalemia being specifically elicited. No supplementary K^+ was administered to any patient in the study.

Results. Mean serum K^+ prior to induction was 4.3 mEq/l. Lowest serum K^+ levels were those immediately after CPB (mean 4.0 mEq/l) and on return to the ward six hours after induction (mean 3.9 mEq/l). From this point in spite of a continued diuresis and no K^+ administration the serum K^+ rose in all patients to achieve a level within normal laboratory limits in all patients but one, (mean at 24 hour post induction 4.9 mEq/l). This was seen in spite of a net loss of K^+ in all patients (mean 80 mEq). No dysrhythmias were seen except in one patient responsive to lidocaine, nor were ECG changes associated with hypokalemia noted.

Discussion. Emphasis has been placed on avoiding hypokalemia in cardiac anesthesia, and the addition of supplementary potassium is advocated in the perioperative period to maintain a normal serum value. Acute hypokalemia during cardiac surgery can result from respiratory alkalosis, hyperglycemia, bicarbonate administration, and diuretics, but this hypokalemia is spontaneously correct in the postoperative period (the K^+ which shifted into cells being given up to the serum). Serum K^+ accounts for 0.5% of total body K^+ and there is a large intracellular reservoir from which acute diuretic losses can be made up. Iatrogenic hyperkalemia from overadministration, or too rapid an administration, of potassium may be a far greater hazard than a transient and self-correcting hypokalemia seen in the normal course of cardiac surgery without supplemental potassium administration and this study suggests that supplemental potassium can be safely omitted in the perioperative period.

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3. Wong KC: ASA Refresher Course Lectures 105:1978.

Title: SUFENTANIL: A DRUG OF CHOICE FOR SPINAL OPIOID ANALGESIA AS SHOWN IN CATS

Authors: M Aoki, M.D., LM Kitahata, M.D., Ph.D., M Senami, M.D., and JG Collins, Ph.D.

Affiliation: Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510

Introduction. The recognition of opioid receptors in the spinal cord and the accessibility of the spinal space by the epidural and intrathecal routes has proven to have significant clinical importance. In spite of the early promise of this newly developed method of opioid administration, various complications have been reported since the inception of spinal opioid analgesia in clinical practice in 1979, respiratory depression and arrest being the most significant. Theoretically, respiratory depression following spinal administration of opioids such as morphine is due to a low lipophilicity which results in large amounts of the drug remaining in the cerebrospinal fluid. Consequently, these high opioid concentrations are capable of ascending toward the brain stem respiratory control centers and reducing respiratory drive. It has been suggested that opioids of higher lipid solubility may be less likely to produce this complication. Sufentanil has a higher lipid solubility than morphine (n-octanol/water partition coefficient = 3.95 for sufentanil and 0.36 for morphine) and thus may be less likely to produce respiratory depression. This study therefore examined the ability of spinally administered sufentanil to block noxiously evoked activity of neurons in the dorsal horn of cat spinal cord. This was done in order to evaluate the possible analgesic effectiveness of spinal sufentanil.

Methods. Cats were anesthetized with a halothane, nitrous oxide, oxygen mixture for surgical procedures which included tracheostomy, arterial and venous cannulation, lumbar laminectomy, and mid-collicular decerebration. Following decerebration, anesthesia was discontinued, and animals were ventilated with $F_IO_2 = 0.21$. Cardiac and respiratory parameters were monitored and kept within physiologic ranges. A tungsten microelectrode with a 10 megohm impedance was advanced into the spinal cord to record extracellular neuronal activity from single wide dynamic range (WDR) neurons. WDR receptive fields on the footpads of the hindpaw were stimulated by noxious radiant heat (51°C) which was focused on the center of the receptive field. Following control studies, the normal saline which had been bathing the spinal cord was removed, and sufentanil, 2.5 and 5.0 ug, dissolved in 0.5 ml of physiologic saline, was applied gently to the spinal cord. I.V. naloxone (0.1 mg) was administered 30 minutes later.

Results. The noxiously evoked activity of all WDR neurons studied was significantly suppressed by spinally administered sufentanil. Suppression was seen within 3 minutes of drug administration, and maximum suppression occurred approximately 30 minutes after administration of sufentanil (activity was suppressed to 55% and 20% of control values by 2.5 μg and 5 μg doses, respectively). Recovery to approximately 80% of control values occurred within 80 minutes following the spinal administration of 2.5 μg of sufentanil. Recovery following the 5 μg dose took much longer. Naloxone reversal following intravenous administration (0.1 mg) was demonstrated.

Discussion. The results of the present study have demonstrated a dose-dependent naloxone reversible suppression of WDR neurons following spinal administration of sufentanil. The suppression of noxiously evoked activity compares very favorably with suppression produced by other opiates that have been shown to produce excellent spinal opioid analgesia. Sufentanil's relatively high lipophilicity should result in less drug remaining in the CSF and thus reduce the potential for respiratory depression. The duration of action was relatively long, probably due to its strong receptor affinity. This study suggests that in light of the significant suppression of noxiously evoked activity by a relatively lipid soluble, long acting drug, sufentanil may be a desirable drug of choice for spinal opioid analgesia.

(Supported by NIH Grant NS-09871)

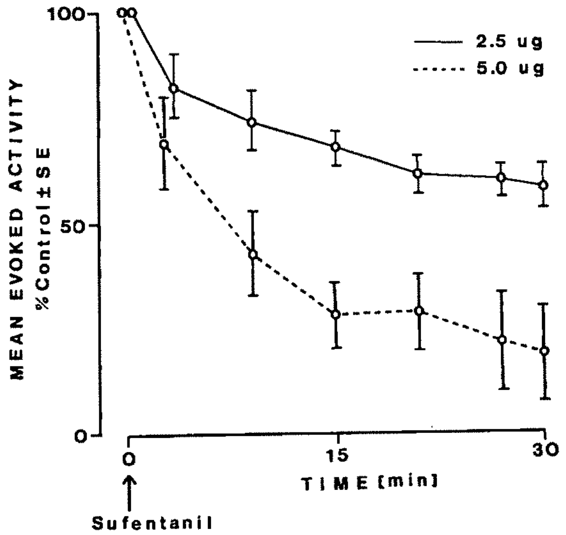

Fig. 1
The effect of spinal sufentanil on the noxiously evoked activity of WDR neurons (n=7 for both 2.5 and 5 μg).

Title: ATRACURIUM IN CARDIAC SURGICAL PATIENTS: CLINCIAL PHARMACOLOGY OF ATRACURIUM IN PATIENTS UNDERGOING SURGERY FOR CORONARY ARTERY DISEASE

Authors: C. Athanasiadis, M.D., C.T. Skourtis, M.D., N.R. Fahmy, M.D., D.G. Lappas, M.D., H.H. Ali, M.D.
Affiliation: Department of Anesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, Massachusetts 02114

Introduction: The present study was undertaken to obtain quantitative assessment of the neuromuscular effect of Atracurium in patients undergoing surgery for revascularization of the myocardium and to evaluate a protocol to shorten the onset time required to achieve 95% single twitch suppression (STS).

Method: Ten patients (ASA III, 40-60 years old), scheduled for coronary artery by-pass grafting (CABG), divided randomly into two groups of five each (Group A and B), were premedicated with morphine 0.1 mg/kg, scopolamine 0.3 to 0.4 mg I.M. and loarzepam 1 mg p.o. In addition to the standard hemodynamic monitoring for CABG, the neuromuscular blockade was monitored by recording evoked thumb adduction in response to supramaximal ulnar nerve stimulation at the wrist(at a frequency of 0.15 Hz). Group A patients received a pretreatment dose of Atracurium 0.05 mg/kg followed 5 minutes later by a bolus injection of 0.35 mg/kg fentanyl 0.05 mg/kg was simulataneously injected via an infusion pump within 5 minutes. In Group B, the pretreatment dose was 0.1 mg/kg and the bolus 0.3 mg/kg given in the same way as in Group A. The time from the second dose of Atracurium to 95% STS was measured. Incremental doses of 0.1 mg/kg atracurium were given each time the twitch response recovers to 10%. The time between the incremental doses was measured and the results were grouped regarding the pre-, intra- and post cardiopulmonary by-pass period (CPB). The patients were also regrouped into two subgroups I and II depending on whether they were receiving propranolol or not. Core temperature was measured via an oesophageal probe. Results were compared using student's t-test for impaired data. Changes were considered significant when p 0.05.

Results: In Group B, 3 patients who were pretreated with 0.1 mg/kg atracurium had a 10% twitch depression and 2 of them were slightly agitated. Excellent intubating conditions were obtained in both groups following a total dose of 0.4 mg/kg and rigidity was not observed. The onset time to 95% twitch inhibition in Groups A and B respectively did not statistically differ. The time from injection to 10% recovery in Group II (propranolol) was 45.0±2.8 min significantly larger than Group I (no propranolol) 28.4±4.9 ($p < 0.001$). The course of the anesthetic with pre- and intra-CPB as shown in Table 1.

Discussion: Pretreatment did not appear to speed the onset time. In fact, it did slow it down when compared with 0.05 mg/kg with more undesirable subjective symptoms. Our results support the finding of Flynn et al[1] who found a temperature-dependent reduction of infusion rate of atracurium. Hypothermia did prolong significantly the 10% recovery time before bypass when compared with patients who were not on propranolol. This diffeence did appear during the hypothermia and CPB.

Conclusion: Atracurium appears to be a desirable relaxant at a dose of 0.4 mg/kg in cardiac surgical patients. Its neuromuscular blocking activity is prolonged by preoperative medications with the beta blocker propranolol and hypothermic cardiopulmonary bypass.

References:

1. Flynn PJ, et al: The use of atracurium in cardiopulmonary bypass with induced hypothermia.

Table
Time to 10% Recovery
0.1 increments of Atracurium

	Group I	Group II
Pre	n=21	n=16
CPB	x=18.56	x=29.46*min
33.6°C	SD=2.5 min	SD=3.9
CPB	8	6
26°C	x=44.8**min	x=51.66**
	SD=+8.9 min	SD=10.87

*$p<0.001$ (Group I vs Group II)
**$p<0.001$ (Group I-CPB vs Group I pre-CPB)
(Group II-CPB vs Group II-pre CPB)

Title: RAPID CORRECTION OF CHRONIC HYPOKALEMIA IN DOGS

Authors: I. Azar, M.D., S. Thiagarajah, M.D., E. Lear, M.D.

Affiliation: Department of Anesthesiology, Beth Israel Medical Center,
Mount Sinai School of Medicine (CUNY), New York, N.Y., 10003

Introduction. Chronic hypokalemia is common in patients on long term diuretic therapy and it may be the cause of dysrhythmias (1), particularily during anesthesia. Preoperative correction of the hypokalemia may require several days because of depletion of intracellular stores of potassium. However, on occasion surgery is urgent and the hypokalemia must be corrected rapidly. The following is a study of serial serum potassium level determinations during rapid correction of chronic hypokalemia in dogs.

Method. The protocol for this study was approved by the institutional committee on scientific activities. Eleven mongrel dogs weighing 20-25 Kg were given furosemide 20 mg im daily and were fed low potassium diet for at least two weeks. When the potassium fell below 3 meq/L, rapid correction of the hypokalemia was achieved as follows: After establishing a peripheral intravenous line the dog was anesthetized with thiopental 30 mg/Kg and the trachea was intubated. Ventilation was maintained mechanically with end-tidal CO2 at about 6%. A femoral artery was canulated for continuous arterial pressure monitoring and blood gas determinations. Arterial blood gases were determined every 30 minutes and metabolic acidosis was corrected with sodium bicarbonate. The lead II of the EKG was monitored and recorded continuously. Rectal temperature was maintained at 38 degrees centigrade. After a period of stabilization a total of five doses of potassium chloride 1 meq/Kg were administered by pump. Each dose was administered in 15 minutes and followed by serum potssium determinations, once every five minutes during a 30 minute period. The serum potassium level at 30 minutes after the completion of each administration of potassium was compared to the baseline value and analyzed statistically using paired t-test. P values less than 0.05 were considered significant.

Results. The results are summarized in the Table and Figure. Following each dose of potassium the serum potassium level rose and declined sharply and reached a plateau with 30 minutes. There was no significant rise in serum potassium at plateau level until after a total of 3 meq/Kg of potassium were administered. Serum potassium at plateau level did not rise above 3 meq/L until after a total of 5 meq/Kg of potassium were administered.

Discussion and Conclusion. A significant depletion of intracelluar potassium occurs during long term administration of diuretics. For every 1 meq/L decrease in serum potassium level the intracellular potassium level may decrease by 35 meq/L. Potassium administration raises serum potassium level rapidly, however following a period of equilibration the serum potassium level decreases sharply. We recommend that following potassium administartion serum potassium level be determined no earlier than 30 minutes after the completion of the administration.

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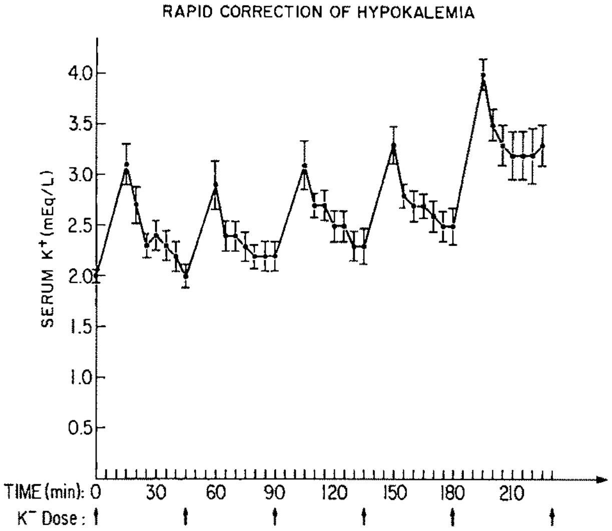

Figure: Serum potassium levels (mean+SE) following repeated doses of potassium 1 meq/Kg in chronic hypokalemia.

	Basline	1st Dose	2nd Dose	3rd Dose	4th Dose	5th Dose
Mean	2.0	2.0	2.2	2.3	2.6	3.3
SD	0.2	0.4	0.5	0.6	0.5	0.7
P	-	NS	NS	0.03	0.004	0.002

Table. The serum potassium level (meq/L) at baseline and 30 minutes after each dose of potassium 1 meq/Kg in chronic hypokalemia dogs.

Title: THE ARRHYTHMOGENIC DOSE OF EPINEPHRINE IN CHRONIC HYPOKALEMIC DOGS

Authors: I. Azar, M.D., S. Thiagarajah, M.D., E. Lear, M.D.

Affiliation: Department of Anesthesiology, Beth Israel Medical Center,
Mount Sinai School of Medicine (CUNY), New York, N.Y., 10003

Introduction. Chronic hypokalemia is common in patients on long term diuretic therapy, and it may be the cause of arrhythmias, particularily during anesthesia. A recent report suggests that hypokalemic patients tolerate anesthesia well and that preoperative correction of the hypokalemia is not essential (1). However, the incidence of arrhythmia in hypokalemic subjects under adverse conditions such as intense sympathetic activity has not been reported. In this study we determined the arrhythmogenic dose of epinephrine before and during rapid correction of chronic hypokalemia in dogs.

Method. The protocol for this study was approved by the institutional committee on scientific activities. Eleven mongrel dogs weighing 20-25 Kg were given furosemide 20 mg im a day and were fed low potassium diet for at least two weeks. When the serum potassium fell below 3 meq/L, the arrhythmogenic dose of epinephrine was determined as follows: After establishing a peripheral intravenous line the dog was anesthetized with thiopental 30 mg/Kg and the trachea was intubated. Ventilation was maintained mechanically with end-tidal CO2 at about 6%. A femoral artery was canulated for continuous arterial pressure monitoring and blood gas determinations. Blood gases were determined every 30 minutes and metabolic acidosis was corrected with sodium bicarbonate. The lead II of the EKG was monitored and recorded continuously. Rectal temperature was maintained at 38 degree centigrade. After a period of stabilization the serum potassium level was determined and then epinephrine 15 ug/Kg/min was administered intravenously by pump until a run of two or more premature contractions was observed. When this occurred the administration of epinephrine was promptly discontinued and the time to return of normal sinus rhythm was determined. After a period of stabilization five doses of potassium chloride 1 meq/Kg each were administered intravenously by pump. Each dose was administered in 15 minutes and then followed 30 minutes later by an epinephrine challange, as described above. The serum potassium levels and the respective arrhythmogenic doses of epinephrine and time to return of normal sinus rhythm were analyzed statistically using regression lines and analysis of variance. P values less than 0.05 were considered significant.

Results. The results are summarized in the Figure and Table. The correlation between serum potassium level and the arrhythmogenic dose of epinephrine, as well as the time to return of normal sinus rhythm, was poor. However, the analysis of variance suggested an association between the two variables: As serum potassium rose, the epinephrine arrhthmogenic dose tended to rise too.

Discussion and Conclusions. This study suggests that hypokalemia decreases the threshold to epinephrine induced arrhythmia and that correction of the hypokalemia raises the threshold. Since endogenous release of catecholamines occurs commonly during anesthesia and surgery, the preoperative correction of the hypokalemia may offer protection against arrhythmias during surgery.

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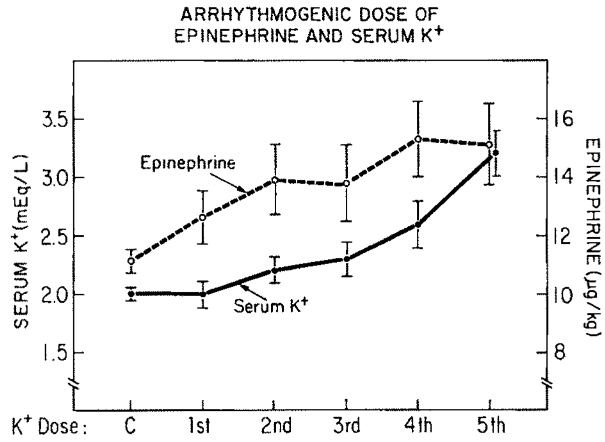

Figure. Serum potassium level and the arrhythmogenic dose of epinephrine during control period (C) and following repeated doses of potassium 1 meq/Kg.

Total K+ Administered	Serum Potassium meq/L	Epinephrine ug/Kg
0 meq/L	2.0+0.2	1.4+1.3
1 "	2.0+0.4	12.6+3.0
2 "	2.2+0.4	13.9+3.8
3 "	2.3+0.5	13.8+4.3
4 "	2.6+0.7	15.3+4.5
5 "	3.2+0.7	15.1+4.6

Table. The arrhythmogenic dose of epinephrine and the corresponding potassium serum level during rapid correction of hypokalemia (mean+SD).

Title: HEMODYNAMIC CHANGES WITH PRONE POSITIONING DURING GENERAL ANESTHESIA

Authors: JE Backofen, M.D., JF Schauble, M.D.

Affiliation: Department of Anesthesiology/Critical Care Medicine, Johns Hopkins
Medical Institutions, Baltimore, Maryland 21205

Introduction. Studies of hemodynamic changes associated with the use of the prone position during general anesthesia are limited to a few reports of decreased central venous pressure.[1] The present review was undertaken to provide a more complete characterization of cardiovascular function in anesthetized prone patients in order to help define risk factors and improve intraoperative management.

Methods. A review of patients with pulmonary and cardiovascular disease, monitored with arterial and thermodilution pulmonary artery catheters, identified 16 patients who had been turned into the prone position during general anesthesia. Mean age of the patients was 65 ± 12 years ($\bar{X}$ ± SD). Operative procedures included: lumbar laminectomy in 8 patients, cervical laminectomy in 4 patients, posterior fossa craniotomy in 1 patient, adrenalectomy in 1 patient, insertion Harrington rod in 1 patient, thoracic laminectomy in 1 patient.

The hemodynamic variables measured included systemic arterial pressure (SAP), right atrial pressure (RAP), pulmonary artery occluded pressure (PAoP), and heart rate (HR), as well as the derived indices of stroke volume (SV), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and cardiac index (CI). Pressure transducers were referenced to the mid-axillary line at the fourth intercostal space. Cardiac output was determined by thermodilution. Measurements were made after induction of anesthesia with the patient in the supine position and repeated after turning the patient into the prone position. The interval between hemodynamic measurements in the supine and then in the prone position was relatively brief, 19 ± 8 minutes; no significant changes in anesthetic agents occurred during this time period. Measurements obtained in the supine and prone positions were compared using Student's paired T test.

Results. The hemodynamic variables and derived indices for the 16 patients are noted in Table I. A prominent finding is the marked decrease in cardiac index in 15 of the 16 patients after being turned into the prone position. This was primarily a reflection of the decrease in stroke volume from 75 ± 20 to 58 ± 16 as heart rate was little changed. SVR and PVR increased in 14 and 13 patients respectively. There were no significant changes in mean systemic arterial pressure, RAP or PAoP in these patients.

TABLE I

		SUPINE	PRONE
C.I.	$l/min/m^2$	2.71 ± 0.52	2.05 ± 0.40*
HR	beats/min	65 ± 16	66 ± 16
PAoP	mmHg	12 ± 4	12 ± 4
RAP	mmHg	8 ± 4	9 ± 4
SVR	dyne sec cm^{-5}	1200 ± 232	1624 ± 388*
PVR	dyne sec cm^{-5}	124 ± 64	164 ± 60*
SV	ml/beat	75 ± 20	58 ± 16*
SAP	mmHg	77 ± 12	79 ± 12

n=16
All Values: Mean ± SD
*P<.01 – compared to supine

Discussion. Turning anesthetized patients from the supine to the prone position resulted in a significant decrease in stroke volume and cardiac index. Since RAP and PAoP changed little, intravascular pressure measurements do not reflect the decreased ventricular preload which has been the focus of most discussion of the hemodynamics of the prone position. Careful support of the patients was employed in an attempt to prevent venous pooling due to compression of the abdomen and of the femoral veins. Nonetheless, it must be recalled that considerable changes in venous flow can occur without there being significant changes in either peripheral or central venous pressure.[2]

The fall in cardiac index upon turning the patients to the prone position is primarily a result of decrease in stroke volume. Systemic arterial pressure is maintained by peripheral vasoconstriction as evidenced by the increase in SVR. There was also a significant increase in pulmonary vascular resistance associated with the fall in cardiac output.

The findings of this review indicate marked decrease in stroke volume and cardiac output associated with turning patients under general anesthesia into the prone position. The extent of this change in cardiac function was identified in this series of patients by measurement of cardiac output and would not be disclosed by consideration of central venous pressure measurements. Patients with borderline clinical status and evidence of hypoperfusion or congestive failure may not tolerate the changes documented in this study and would benefit from use of pulmonary artery thermodilution catheters and measurement of cardiac output if the prone position is to be used during anesthesia.

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2. Folkow B, Mellander S. Veins and Venous Tone. Am Heart J 68:397-408, 1968.

Title: HEMODYNAMIC EVENTS ASSOCIATED WITH REGIONAL ANESTHESIA FOR CAROTID ENDARTERECTOMY

Authors: FJ Balestrieri, M.D., DS Prough, M.D., EH Stullken, M.D., CH Davis, Jr., M.D., JM McWhorter, M.D., G Howard, M.S.P.H.

Affiliation: Departments of Anesthesia and Neurology, and Section on Neurosurgery, Department of Surgery, Wake Forest University, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103

Introduction. Large hemodynamic changes commonly occur during and after anesthesia in patients undergoing carotid endarterectomy. Such changes may be sufficient to produce myocardial ischemia in this group of patients with a high incidence of cardiovascular as well as cerebrovascular disease (1). The increase in blood pressure (BP) seen with carotid cross-clamping (CCC) is similar in magnitude to that seen with infrarenal aortic cross-clamping during aortic surgery (2). The BP during CCC may be higher with regional anesthesia than with general anesthesia. Although hypertension and hypotension are common postoperatively (1), the incidence of overt myocardial infarction is low after regional anesthesia (3). To clarify the hemodynamic course of carotid endarterectomy performed under regional anesthesia, we used pulmonary artery catheterization to study prospectively: 1) the hemodynamic consequences of CCC, and 2) the hemodynamic basis for postoperative changes in BP.

Methods. Thirteen patients consented to participate in a protocol approved by the Institutional Research Practices Committee. Anesthetic management included diazepam 0.1 - 0.15 mg/kg po preoperatively, superficial cervical plexus blockade with 0.5% bupivacaine supplemented by small iv doses of diazepam and fentanyl. At six intervals--pre-anesthesia (P), incision (I), at peak BP during CCC, in the immediate recovery period (R), and in the Intensive Care Unit 4 hours (ICU-4) and 14 hours (ICU-14) after operation--we measured systolic, diastolic, and mean arterial pressure (MAP); pulmonary artery systolic, diastolic, and mean pressures; pulmonary artery occlusion pressure (PAOP); cardiac output (CO); central venous pressure; and heart rate, and we calculated systemic vascular resistance (SVR).

Phenylephrine was used postoperatively to maintain systolic BP at > 120 mmHg except in patients whose preoperative systolic BP had been < 120 mmHg. Data were analyzed using multivariate analysis of variance of repeated measures with $p < 0.05$ being considered significant.

Results. Hemodynamic events at the six intervals are shown in the figure. MAP was higher at CCC than at P and lower in the ICU than at P. CO was higher during CCC, and PAOP tended to be higher during CCC. PAOP was significantly lower in the ICU than preoperatively ($p < 0.05$). Three of the 13 patients experienced substantial increases in PAOP during cross-clamping.

Discussion. Regional anesthesia is associated with a significant increase in BP during CCC and a significant decrease in BP in the ICU, despite the administration of phenylephrine to 11 of 13 patients. The reduction in MAP cannot be explained by changes in CO or SVR alone, although both appear to be contributory. The increase in MAP during CCC appears to be the result of an increase in CO and, in 3 patients, it caused an increase in PAOP. Postoperative hypotension appears to reflect mild vasodilation, perhaps because of increased perfusion pressure at the carotid sinus, and a clinically unimportant reduction in CO. A mean PAOP of < 6.0 mmHg at R supports the contention that volume expansion might be effective therapy (4). Despite infusion of a vasoconstrictor to elevate BP, no signs of hyperperfusion developed in the patients in this series.

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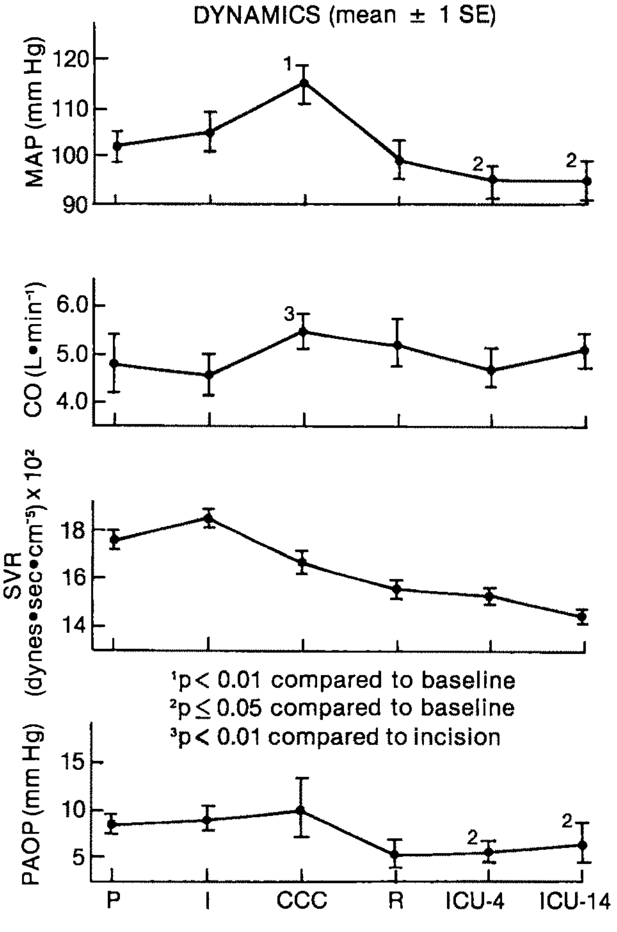
REGIONAL ANESTHESIA FOR CAROTID ENDARTERECTOMY: PERIOPERATIVE DYNAMICS (mean ± 1 SE)



Title: SPINAL ANESTHESIA IN PEDIATRIC SURGERY

Authors: G Blaise and L Roy

Affiliation: Department of Anaesthesia, The Hospital for Sick Children, Toronto, Ontario, Canada

Introduction. Spinal anesthesia is not common in pediatric surgery; however, it could be a valuable alternative to general anesthesia for pediatric patients booked for short procedures (less than 60 minutes) (1).

Material and Method. We have used spinal anesthesia for orthopedic procedures (tendon release of lower extremities, club foot surgery, hip surgery, resection popliteal cyst, etc.) or low abdominal surgery (hernia repair, orchidopexia). With parents' consent, we used the technique in 30 patients--18 had orthopedic procedures, 12 had abdominal surgery. The smallest child was 7 weeks old at 3.7 kg, expremature for hernia repair. The oldest child was 13 years old for orthopedic surgery.

Technique. In young children (less than 9 years old) we used the hollow stylette of a 24 angiocath (27-gauge needle - Cat. No. 38-2818-5, Deseret Medical Inc., Parke-Davis Company, Sandy, Utah 84070 USA); in older children we used the stylette of a 20 angiocath (23-gauge needle). The spinal anesthesia was done mainly on a child sitting on the O.R. table. For patients older than 2 years old, we tried to fix their attention by telling stories, reading books, or showing them a movie for children on a V.C.R. machine (Walt Disney cartoon). We continued the show for the duration of the procedure. In very few circumstances did we use the lateral position to do spinal anesthesia.

Results (Tables 1, 2). Eighteen patients received bupivacaine (2) spinal anesthesia for orthopedic surgery. Thirteen received no sedation or minimal sedation (Fentanyl 2 µg/kg, diazepam 0.1 mg/kg). Five patients need a light general mask anesthesia (N_2O 70%/O_2 30%; halothane 0.5%)--one 15 minutes after the induction, four at the end of the procedure (duration of surgery was too long). Two patients received bupivacaine spinal anesthesia for hernia repair, both needed a light general anesthesia because of lack of relaxation.

Ten patients received pontocaine spinal anesthesia for abdominal surgery (hernia repair, orchidopexia, hydrocele). Four of them needed supplementation with a light general anesthesia. These patients complained of pain during surgery (peritoneal traction).

Complications. In four young patients we failed to find the subdural space despite three trials at the beginning of this series. One 2.5-year-old boy had a headache, nausea, and vomiting for 3 days after spinal anesthesia, at which time a 23-gauge needle had been used. We changed to a 27-gauge needle after this complication.

Discussion and Conclusions. Spinal anesthesia is an easy technique in children; the use of a very small needle is not painful. For short peripheral procedures it is an interesting alternative to general anesthesia for children with respiratory diseases (1). With the help of the audiovisual technique (V.C.R. machine), spinal anesthesia could change a stressful surgery to a great experience for children.

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Table 1. Supplementation of spinal anesthesia.

	No sedation	Fentanyl 2 µg/kg Diazepam 0.1 mg/kg	Light G. anesthesia
Ortho. surg. 18 patients	7 patients	6 patients	5 patients
Low abdom. surg. 12 patients	0 patients	6 patients	6 patients

Table 2. Medications and doses used.

Pontocaine (mg/kg)	0-3 months 0.4-0.5	3-24 months 0.3-0.4	>24 months 0.2-0.3
Bupivacaine (mg/kg)	0-24 months 0.3-0.4	>24 months 0.3	
Adrenaline (µg)	<24 months 10	>24 months 20	

Title: A New Concept in Inhaled Anesthetic Pharmacokinetics

Authors: Randall L. Carpenter, Edmond I. Eger II, Brynte H. Johnson, Jashvant D. Unadkat

Affiliation: Department of Anesthesia, University of California, San Francisco, California 94143

Introduction. Currently a 4 compartment model is used to explain the uptake and distribution of inhaled anesthetics. Pulmonary washin of anesthetic is followed by distribution to the vessel rich, muscle, and fat tissues. Evidence for this paradigm of pharmacokinetics comes from our knowledge of tissue blood flow and solubility. Direct measurements of the transfer of anesthetic to or from these tissues are limited. Most studies have examined pharmacokinetics in the immediate perioperative period and thus have not investigated distribution to slowly equilibrating compartments (e.g., muscle and fat). We postulated that such compartments might be defined by anesthetic elimination over a prolonged period.

Methods. After approval from our Committee on Human Experimentation, we established anesthesia with nitrous oxide in 6 healthy paralyzed 42.3 ± 5.3 year old (mean ± SE) patients ventilated to maintain normocapnia. A mixture of isoflurane, enflurane, halothane and methoxyflurane, each at 0.3 MAC, was administered for 2 hours. End tidal, mixed-expired (ME), and inspired (FI) samples were collected during administration and for 5 to 9 days thereafter. Ventilation (VE) was concurrently measured. Gases were analyzed with gas chromatography. We fit a 4 and 5 compartment model to the decay of the alveolar concentration of each anesthetic for each patient during recovery. Uptake and elimination per minute were calculated as VE(FI - ME) and total uptake and elimination calculated. Elimination from each compartment was estimated as the elimination occurring during 3 time constants for that compartment minus the sum of the elimination calculated for compartments having shorter time constants.

Results. In 19 of 24 comparisons a 5 compartment model provided a significantly better fit than a 4 compartment model and these 19 sets of values were used in the subsequent analyses. The half-times for a given compartment for each anesthetic were comparable (Table 1) as were the percentages of anesthetic issuing from each compartment on recovery (Table 2). The amount of anesthetic recovered relative to that administered was isoflurane 92.7±6.3%, enflurane 85.0±6.5%, halothane 49.6±4.1%, and methoxyflurane 25.6±2.7%.

Discussion. Our results are qualitatively consistent with previous data regarding recovery of anesthetic taken up. Our data imply that isoflurane is least metabolized and that the majority of methoxyflurane is metabolized. If we assume that isoflurane is not metabolized and that incomplete recovery is due to loss through skin or the wound, then by normalizing the recovery of each anesthetic to that of isoflurane (100%) we can estimate the loss of the other anesthetic due to metabolism. This suggests a metabolism of enflurane of 8%, of halothane of 46%, and of methoxyflurane of 72%.

Our results are in accord with previous notions regarding a 4 compartment model for uptake and distribution. The short half-time of our first compartment is consistent with that predicted for washin of the lungs. The half-times for the second, third, and fifth compartments likewise are consistent with current data for blood flow and solubility of vessel rich, muscle, and fat groups respectively.

However, we have identified an additional (fourth) compartment with a half-time between that of muscle and fat (Table 1) that accounts for about 1/3 of the anesthetic recovered. We speculate that the fourth compartment is fat with a high blood flow or with access to anesthetic by diffusion from a highly perfused compartment (intertissue diffusion). We speculate further that this tissue is visceral fat. Support for this thesis comes from the differences for halothane versus enflurane or isoflurane in recovery from this compartment. Recovery of enflurane and isoflurane was significantly greater, a finding consistent with their lower metabolism and the fact that some of the blood draining visceral fat must pass through the liver. If our speculation regarding this compartment is correct, then 50% to 60% of the anesthetic taken up eventually lodges in fat.

Table 1: Compartment half-times (min)

Compartment	Isof	Enfl	Halo	Meth
1	.11 ±.02	.09 ±.02	.13 ±.02	.07 ±.00
2	4.11 ±.97	4.11 ±.92	4.62 ±.97	4.89 ±.83
3	53.5 ±8.3	59.0 ±15.8	51.5 ±6.9	48.3 ±4.6
4	386 ±120	347 ±64	324 ±54	369 ±55
5	2430 ±139	2054 ±111	2614 ±130	2120 ±419

Table 2: % of Anesthetic From Each Compartment

Compartment	Isof	Enfl	Halo	Meth
1	1.1 ±.3	0.9 ±.0	1.2 ±.1	3.3 ±1.9
2	13.0 ±3.8	12.0 ±3.4	17.2 ±4.7	19.3 ±8.3
3	27.6 ±1.7	26.2 ±1.7	30.7 ±3.4	29.9 ±6.1
4	31.8 ±2.3	35.4 ±7.2	27.2 ±3.3	27.9 ±4.6
5	26.2 ±3.5	25.6 ±3.4	23.6 ±3.1	21.6 ±4.0

Title: DOES CHRONIC VERAPAMIL (V) TREATMENT AFFECT THE CARDIOVASCULAR EFFECTS OF ANESTHETICS?

Authors: J. Chelly,M.D., K. Rogers,M.D., R.G. Merin,M.D., M-F Doursout, A. Taylor,M.D., C. Hartley, Ph.D.

Affiliation: Departments of Anesthesiology and Medicine, Baylor College of Medicine, Houston, Texas and
Department of Anesthesiology, University of Texas Medical School, Houston, Texas

Introduction. Although the interaction between intravenous V and anesthesia has been investigated, (1,2) in fact the interaction of chronic V dosing and anesthetics is a more important clinical problem. This study was designed to compare the effects of the inhalation anesthetics halothane (Ha), enflurane (E) and isoflurane (I) in chronically instrumented dogs before and after chronic oral V administration.

Methods. Five conditioned dogs were instrumented for measurement of aortic (A), and left ventricular (LV) pressures (P); carotid (Ca) and renal (R) blood flows (BF) using pulsed Doppler flow probes. Experiments were conducted at least 10 days following surgery when the animals were healthy and trained. Anesthesia was induced by mask; ventilation and F_iO_2; end tidal anesthetic concentrations of approximately 1 MAC (L) and 1.5 - 2 MAC (H) were maintained for twenty minutes before measurement of the hemodynamic variables. Anesthetic concentrations were continually monitored by infra-red analysis. Following the anesthetic experiments, the animals were given 80 mg V by mouth tid for 8-10 days. Preliminary experiments showed that this dosing regiment produced a relatively steady plasma (PL) level of V within five days of beginning dosing. One hour following the AM V dose, the anesthetic protocol was repeated as before. 120 mg V per mouth tid was then administered for another 8-10 days and the anesthetic studies again repeated. Statistical analysis compared the hemodynamic effects of L and H anesthesia before and after the 80 mg and 120 mg V dosing using the Bonferroni correction of the paired t test. Mean ± Standard Error are presented.

Results. Mean PL V levels ranged from 73-131 ng/ml after 80 mg V tid and from 175-287 ng/ml after 120 mg.CaBF was not affected by chronic V; although LV dP/dt tended to be lower after chronic V, the only significant differences were in heart rate (HR). MAP and RBF (Table 1). Most of the important differences noted after the verapamil dosing were during either high anesthetic concentrations and/or high PLV levels.

Discussion. The calcium channel blocking drugs of which V is the first, have become a mainstay of therapy for patients with ischemic heart disease. Consequently, many patients are coming to anesthesia and surgery being chronically treated with these drugs. Previous investigations of the interaction between anesthetics and V have looked only at acute intravenous V dosing. For the first time, this study documents the effects of chronic V administration on the hemodynamic effects of anesthetics. In fact, the interaction is remarkably benign. If only 1 MAC concentrations of the anesthetics are considered, then the only significant depression of cardiovascular function produced by V either at the 80 or 120 dose is the decrease in renal blood flow during high dose verapamil and 1 MAC isoflurane anesthesia. There are a number of interactions at high concentrations of verapamil and 1.5-2 MAC anesthesia as can be seen from Table 1. However, this degree of anesthetic depression is rarely achieved in clinical practice today. Consequently, this study would suggest that if high concentrations of the inhalation anesthetics are avoided, patients under chronic verapamil treatment may be safely anesthetized with the inhalation anesthetics.

Table 1

	Ha	E	I
HR (bts/min)			
Awake	95 ± 9	87 ± 5	91 ± 7
L	101 ± 10	108 ± 8	112 ± 8
H	117 ± 13	120 ± 5	113 ± 4
L-80V	98 ± 5	98 ± 9	101 ± 8
H-80V	103 ± 11	105 ± 8	113 ± 4
L 120V	97 ± 5	92 ± 8	100 ± 6
H 120V	97 ± 9*	98 ± 7*	98 ± 10
MAP (mmHg)			
Awake	99 ± 5	97 ± 8	96 ± 4
L	79 ± 4	78 ± 6	83 ± 6
H	54 ± 5	48 ± 3	56 ± 4
L-80V	75 ± 6	77 ± 9	75 ± 4
H-80V	39 ± 3*	54 ± 6	46 ± 7
L-120V	71 ± 5	68 ± 4	82 ± 3
H-120V	34 ± 4*	45 ± 3	42 ± 3*
RBF (ml/min)			
Awake	100 ± 20	108 ± 18	116 ± 22
L	99 ± 18	86 ± 12	112 ± 17
H	101 ± 12	87 ± 13	105 ± 16
L-80V	97 ± 15	90 ± 24	72 ± 5*
H-80V	69 ± 12	84 ± 8	65 ± 7*
L-120V	81 ± 14	76 ± 14	63 ± 11
H-120V	55 ± 24	50 ± 7*	51 ± 5*

* = p<.05 vs without V

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Title: **FLUOSOL-DA PROLONGS INDUCTION OF ISOFLURANE ANESTHESIA IN THE DOG**

Authors: R.T. Chilcoat, Ph.D., J.I. Gerson, M.D. and F.B. Allen, M.D.

Affiliation: Department of Anesthesiology, State University of New York, Upstate Medical Center,
Syracuse, NY 13210

Introduction. Fluosol-DA, an inert aqueous emulsion of perfluorochemicals currently being tested as a plasma expander and oxygen transport fluid, has been shown to dissolve larger amounts of volatile liquid anesthetics than blood and to increase the solubility of these anesthetics in blood. (1,2) These in-vitro findings suggest that induction of anesthesia will be prolonged in patients treated with Fluosol-DA. The present study examines the in-vivo effect of Fluosol-DA 20% (Fluosol) on the rate of rise of F_A/F_I, where F_A is the alveolar tension and F_I is the inspired tension of isoflurane.

Methods. Five mongrel dogs (wt. 22-24 kg) were studied under basal anesthesia (pentobarbital and metocurine). Inhalational anesthesia was induced with isoflurane (1% in oxygen), while recording F_I and F_A (measured by infrared gas analysis). Temperature and end-tidal PCO_2 were held constant. Cardiac output was monitored by thermal dilution. Isoflurane was then washed out to an end-tidal concentration less than .05%. After rapid removal of 750ml of blood from the femoral artery, 1000ml of Fluosol was infused intravenously. Cardiac output was allowed to stabilize for about 2 hours. Propranolol and/or verapamil were used to lower cardiac output further, to near its original value, in four dogs. Isoflurane was then administered a second time under conditions similar to the first. Fluorocrit, the ratio of perfluorocarbons to total volume of a centrifuged blood sample (analogous to hematocrit), was measured. F_A/F_I was plotted against time before and after Fluosol administration. However, because cardiac output was always higher after Fluosol infusion (even after propranolol and/or verapamil), and because this will also delay induction, these curves reflect both effects of Fluosol. To separate the two effects, a physiological computer model of uptake (1) was given the values of cardiac output measured during each experiment and used iteratively to calculate the blood/gas partition coefficient of isoflurane which must have existed in each animal to account for the observed F_A/F_I difference after allowing for observed cardiac output variation. For comparison, "predicted" partition coefficients after Fluosol infusion were calculated by weighted averaging, using individual fluorocrits.

Results. In each animal, F_A approached F_I more slowly after Fluosol. The Figure shows the mean F_A/F_I curves for all animals, before and after Fluosol. Cardiac output was 3.65 ± 0.35 (SD) L/min immediately prior to the first isoflurane inhalation, rose to 8.23 ± 0.69 L/min following phlebotomy and Fluosol infusion, and fell to 5.00 ± 2.45 L/min prior to the second inhalation. Mean fluorocrit was 3.9% ± .7, indicating that approximately 25% of each dog's blood volume was Fluosol. "Actual" pre and post Fluosol partition coefficients, calculated by model fitting, were 1.45 ± .15 and 2.59 ± .51 respectively. The mean of the "predicted" post-Fluosol coefficients, calculated by weighted averaging, was 2.91 ± .36. The pre-and-post-Fluosol coefficients were significantly different ($p < .001$ by analysis of variance), while the "predicted" and "actual" post-Fluosol coefficients were not significantly different from each other.

Discussion. Replacement of 25% of blood volume by Fluosol delays anesthetic induction with isoflurane. As indicated in the Figure, F_A rose to 70% of F_I in about 4 minutes in untreated dogs. The presence of 25% Fluosol tripled this time. Based on their measured blood/gas partition coefficients (1,2) similar, although smaller, delays would be expected with enflurane and halothane. Part of the delay is due to increased cardiac output, which was seen consistently following phlebotomy and Fluosol infusion. A 33% increase in cardiac index has also been observed following infusion of 500ml of Fluosol in humans. (3) However, even after increases in cardiac output were allowed for, the model required a significantly increased blood/gas partition coefficient to account for the observed delay, and this coefficient was not different from that predicted. Prolongation of induction in humans given Fluosol would therefore be expected due to increases both in anesthetic blood solubility and in cardiac output.

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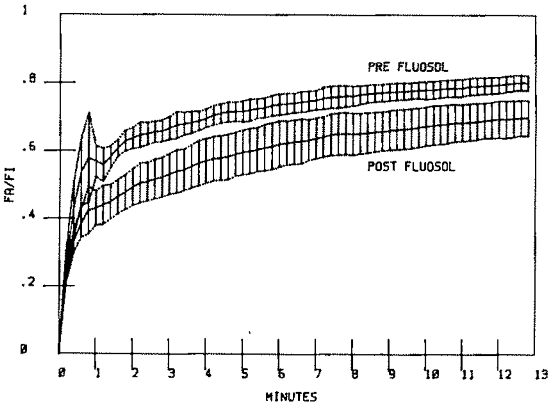

Figure. Alveolar(F_A)/Inspired(F_I) ratio during inspiration of 1% isoflurane before and after administration of Fluosol-DA. Graphs are means of five experiments. Bands indicate + 1 SD.

Title: TRANSCUTANEOUS OXYGEN MONITORING DURING ENDOBRONCHIAL THORACIC ANESTHESIA

Authors: NM Chubra-Smith, M.D., RP Grant, M.D., and LC Jenkins, M.D.
Affiliation: Department of Anesthesia, Vancouver General Hospital, Vancouver, British Columbia, and University of British Columbia, Vancouver, British Columbia

Introduction. Previous studies have shown transcutaneous oxygen (PtcO2) correlates well with arterial oxygen tension (PaO2) (1). During endobronchial anesthesia hypoxemia may occur from intrapulmonary shunts, altered hypoxic pulmonary vasoconstriction, absorption atelectasis and surgical impairment of ventilation or cardiac output (2). This study examines the relationship between PtcO2 and PaO2 during endobronchial anesthesia for pulmonary resection.

Methods. Human Ethics Committee approval was obtained and after written informed consent, 30 patients aged 41 to 76 years scheduled for elective lobectomy or pneumonectomy were studied. For each patient, inspired oxygen (FiO2), PtcO2, PaO2, heart rate (HR), mean arterial blood pressure (MAP) and temperature were recorded. Baseline assessments on room air and supplemental oxygen were done preoperatively (preop). Measurements were taken every 15 minutes intraoperatively during endotracheal (ET) and endobronchial (EB) ventilation. The FiO2 was varied according to the patient's clinical condition. PtcO2 was allowed to stabilize for 10 minutes before arterial blood samples were drawn through an indwelling radial artery catheter. PtcO2 was measured using a Lifespan 100 transcutaneous oxygen/carbon dioxide monitor (Biochem International, Waukesa, WI) and PaO2, using a Radiometer ABL 3 analyzer (Copenhagen, Denmark). All patients received a standard anesthetic with isoflurane, nitrous oxide, fentanyl and pancuronium. All underwent endobronchial intubation after induction. Data were analyzed using the Pearson correlation coefficient and regression analysis. The transcutaneous oxygen index (3) (tcO2 index) was calculated for each group and compared using t-tests. A $p<0.05$ was considered significant.

Results. There were 19 males and 11 females studied. Mean age ± SD was 63.5 ± 10.2 years. Eight pneumonectomies and 22 lobectomies were performed. There were 347 paired PtcO2/PaO2 measurements, with 56 in the preop, 159 in the ET and 132 in the EB groups. There was a significant correlation between PtcO2 and PaO2 in all groups: $r = 0.97$ (preop), 0.91 (ET) and 0.83 (EB). The regression between PtcO2 and PaO2 during ET ventilation was given by PtcO2 = -4.32 + 0.70PaO2, and during EB ventilaion, by PtcO2 = 21.36 + 0.47PaO2. The tcO2 indices were 0.69 ± 0.09 (preop); 0.68 ± 0.10 (ET); 0.61 ± 0.14 (EB) ($\bar{x}$ ± SD). The tcO2 index during EB ventilation was significantly lower than the preop and ET groups. No correlations between tcO2 index and PaO2, MAP or temperature were found in any group. The tcO2 index overestimated PaO2 from PtcO2 (>10 torr) in 69% of measurements and underestimated PaO2 in 22% (<10 torr). The 90% response time of PtcO2 to changes in FiO2 was 118 ± 64 seconds ($\bar{x}$ ± SD). PtcO2 changed in the same direction as PaO2 in 88% of the measurements, in the opposite direction in 7%, and did not change in 5%. All 347 PtcO2 readings were below the corresponding measured PaO2. In four patients a precipitous drop in PtcO2 was noted within 4 minutes of initiating EB ventilation, despite the FiO2 being 1.0. In 3 patients this drop corresponded with marked hypoxemia (PaO2 < 45 torr). In the fourth patient the drop in PtcO2 was associated with hypotension (MAP 32 torr), no change in PaO2, and subsequent ST elevation on the electrocardiogram. In all 4 patients, the PtcO2 was the first monitored parameter to change, indicating a change in clinical status of the patient.

Discussion. The present study confirms the correlation between PtcO2 and PaO2 during endotracheal anesthesia for thoracotomy (4), and demonstrates the sustained correlation during endobronchial anesthesia. The lower tcO2 index during endobronchial anesthesia suggests a change in the relationship between PtcO2 and PaO2 during one-lung ventilation which is not obviously related to FiO2, PaO2, MAP or temperature differences. The tcO2 index could have dropped as a result of changes in cardiac output (3) associated with altered pulmonary blood flow during endobronchial ventilation and/or surgical manipulation, however cardiac output was not measured in this series of patients. As the monitored PtcO2 was consistently lower than the measured PaO2, continuous recording of PtcO2 provided valuable estimation of a "minimum" PaO2 level throughout pulmonary resection. PtcO2 monitoring proved also to act as an early warning device for impending hypoxemia and hemodynamic compromise, thereby facilitating very early therapeutic intervention. This holds special relevance during endobronchial anesthesia for thoracotomy, where there is a substantial risk of developing hypoxemia.

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TITLE: PEEP DURING ONE LUNG ANESTHESIA IMPROVES OXYGENATION IN PATIENTS WITH LOW ARTERIAL PaO_2

AUTHORS: E Cohen MD, DM Thys MD, JB Eisenkraft MD, JA Kaplan MD

AFFILIATION: The Department of Anesthesiology, The Mount Sinai School of Medicine, One Gustave Levy Place, New York City, NY 10029

INTRODUCTION During one lung anesthesia (OLA) for thoracic surgery, arterial oxygenation (PaO_2) may be compromised due to V/Q abnormalities. Application of CPAP with 100% oxygen to the non-ventilated lung and/or PEEP to the ventilated lung have been tried in an effort to improve PaO_2.[1] Previous studies[1-3] showed that CPAP alone or in combination with PEEP improved oxygenation, while the application of PEEP alone may either decrease PaO_2 or have no significant effect on oxygenation. The most likely mechanism is an increase in shunting through the collapsed lung caused by the positive pressure in the ventilated lung when PEEP is applied. The purpose of this study was to further evaluate the effect of PEEP (10 cm H_2O) on PaO_2 and cardiac output (CO) during OLA.

METHOD After institutional approval, eighteen patients ASA 1 or 2 undergoing thoracotomy for pneumonectomy or lobectomy were studied. Monitoring was established with a radial artery cannula and an Oximetrix Opticath PA® catheter. Anesthesia was induced with thiamylal sodium 3.5 mg/kg. Endobronchial intubation with a Robertshaw double lumen tube was facilitated by succinylcholine 1 mg/kg. Anesthesia and relaxation were maintained with N_2O/O_2 (50/50%), isoflurane 1.0-1.5% (inspired concentration), and pancuronium. Arterial blood gases and hemodynamic parameters were measured 15 minutes after stabilization had occurred following onset of 1) one lung anesthesia, and 2) application of $PEEP_{10}$ cm H_2O to the ventilated lung. The mixed venous oxygen saturation (SVO_2) was monitored continuously. Temperature and hemoglobin were kept within the normal range. Results are expressed as mean ± standard deviations. Statistical significance of differences among the groups was assessed using the Student's t-test.

RESULTS Overall, the application of $PEEP_{10}$ did not produce a significant improvement in PaO_2 (from 80 ± 26 to 108 ± 50 mmHg). There was a non-significant reduction in CO (from 4.9 ± 1.3 to 4.3 ± 1.1 L/min), while the SVO_2 remained unchanged (77 ± 6 to 76 ± 6%). The PaO_2 values for each of the 18 patients during OLA alone and with the application of $PEEP_{10}$ are shown in the table. Of the 18 patients, 13 patients showed an improvement in PaO_2 during the application of PEEP. Ten of these 13 patients were relatively hypoxic during OLA (PaO_2 below 80 mmHg). Furthermore, 4 out of the 5 patients who had a PaO_2 deterioration during the application of PEEP had a PaO_2 above 80 mmHg during OLA. When evaluating only those patients with PaO_2 below 80 mmHg during OLA, the application of PEEP improved PaO_2 in 10 out of 11 patients and the overall PaO_2 values significantly increased from 64 ± 6 to 87 ± 3 mmHg. The SVO_2 of these 10 patients remained unchanged (from 77 ± 5 to 76 ± 4%) in spite of a significant reduction in CO (from 5 ± 1.1 to 3.9 ± 1 L/min).

DISCUSSION Overall, the application of PEEP produced no significant improvement in PaO_2, CO, and SVO_2, as compared with OLA alone. However the relatively hypoxic patients with PaO_2 below 80 mmHg showed an increase in PaO_2 upon the application of PEEP. Katz et al[2] and Tarhan et al[3] have previously shown that although their total patient groups showed no benefit in PaO_2 with PEEP, there were two patients in each study that did benefit from PEEP. These patients were distinguished from the others by having a PaO_2 less than 80 mmHg prior to the application of PEEP. These authors[2,3] used 100% oxygen in their studies and, therefore, the patient's mean PaO_2 values during OLA were mostly above 100 mmHg. Because we used 50% oxygen in our study, 11 out of 18 patients had a PaO_2 below 80 mmHg. However, 10 of these 11 patients benefited from PEEP. Therefore, we postulate that in patients with a PaO_2 above 80 mmHg, application of PEEP may interfere with pulmonary blood flow distribution by diverting blood to the non-ventilated lung. This may disrupt the existing V/Q balance and result in a deterioration of PaO_2. However, in patients with a PaO_2 below 80 mmHg, the application of PEEP may reduce the degree of atelectasis in the ventilated lung resulting in a more favorable V/Q balance and an improvement in PaO_2. The SVO_2 remained stable despite the significant decrease in CO because oxygen delivery to the periphery was maintained. The observation that CO decreased when PaO_2 improved in these patients reinforces the possible negative correlation existing between CO and PaO_2. We conclude that the application of PEEP is beneficial in those patients who become relatively hypoxic (PaO_2 below 80 mmHg) during OLA.

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TABLE

The PaO_2 value of each patient during OLA and the application of PEEP.

Pts with PaO2<80mmHg		Pts with PaO2>80mmHg	
OLA	$PEEP_{10}$	OLA	$PEEP_{10}$
73	125	121	258
65	69	135	170
76	94	117	140
54	59	114	73
53	57	102	86
66	125	111	73
64	67	93	86
64	74		
62	81		
72	151		
64	58		

Title: MAGNESIUM PRE-TREATMENT AT C-SECTION FOR PREGNANCY-INDUCED HYPERTENSION

Authors: R.C. Cork, M.D., Ph.D., and M.F.M. James, M.B., Ch.B., FFARCS

Affiliations: Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724
and the Department of Anaesthetics, University of Zimbabwe, Harare, Zimbabwe

Introduction

Risk of rapid-sequence induction for patients with uncontrolled pregnancy-induced hypertension (PIH) is compounded by the extreme hypertension present at induction. The stress of laryngoscopy and intubation increases an already high blood pressure and puts the patient at risk for cerebral hemorrhage, which is the most common cause of death in PIH. Dandavino et al. have shown that the hemodynamic effects of a bolus of magnesium, although beneficial, are transient, lasting only 5-10 minutes (1). The purpose of this study was to examine the effect of a bolus of magnesium at induction of anesthesia in attenuating the hypertensive response to laryngoscopy and intubation in patients with uncontrolled PIH.

Methods

Permission for the study was granted by the Ethics Committee. After informed consent, 14 patients with PIH were randomly assigned to a magnesium group (MG) or a control group (CNTRL). PIH was defined as a systolic BP over 140 torr or a rise above normal of 30 torr or a diastolic BP above 90 torr or a rise above normal of 30 torr. Also, urine proteinuria (1+ to 4+) and onset after 20 weeks gestation were required for entry into the study. Patients were brought into the operating room, where ECG leads and BP cuffs were placed and a second i.v. line for blood sampling was started. Baseline blood pressure and pulse were taken by the anesthesiologist, who was blind to which group the patient belonged. Pre-oxygenation and the delivery of the pre-treatment drug (magnesium 60 mg/kg or Ringer's Lactate) were carried out over 3 min. BP and pulse were then taken and a blood level for magnesium was drawn. Rapid-sequence induction was performed on all patients with thiopental (250 mg), succinylcholine (100 mg), and cricroid pressure. Two minutes after laryngoscopy and intubation, BP and pulse were recorded and blood was drawn for magnesium levels. Any dysrhythmias were noted. At delivery, BP and pulse were recorded and blood for magnesium levels was obtained from both the mother and the umbilical cord. Minimum and maximum BP and associated pulse rates were noted before and after delivery. Muscle relaxation for all patients was achieved with alcuronium 10-20 mg as needed. Statistical analysis was with Student's t-tests for grouped and paired data with the Bonferonni adjustment for multiple comparisons, and with chi-square analysis. Significance was defined as $p < 0.05$.

Results

For the 14 patients (7 MG and 7 CNTRL) studied, mean age was 21.6 ± 1.4 (SEM) and ranged from 17 to 35. All of the control group were nulliparous, but 3 of the MG group were parity 1, 2, and 4, respectively. None of the patients with parity > 0 had a history of PIH. Three of the MG group and 1 of the CNTRL group had fitted prior to coming to the operating room. There was not history of heart, lung, or renal disease in any of the patients. Three fetuses in each group were in distress as demonstrated by auscultated late decelerations of heart rate. None of the patients had been treated with magnesium. Five of the MG group and 2 of the CNTRL Group had been treated with diazepam (15 to 40 mg), and 5 of the MG Group and 4 of the CNTRL Group had received hydralazine (6.5 to 37.5 mg). Baseline systolic pressure, diastolic pressure, and pulse on admission to the operating room were 175.0 ± 5.3 torr, 114.3 ± 5.0 torr, and 112 beats/minute, respectively. There was no significant difference between groups in baseline variables. Only 1 patient exhibited dysrhythmias (multifocal PVC's in the CNTRL Group). Changes in systolic BP (SBP), diastolic BP (DBP) and pulse rate were noted in the TABLE, as are the mean serum mg levels after pre-treatment, after intubation, and at delivery. There were no significant differences between groups in minimum and maximum SBP, DBP, and pulse, before and after delivery. No difficulty with prolonged neuromuscular blockade was found in the MG group. One-minute APGAR score was 6.4 ± 0.9 for the MG Group, 4.6 ± 1.0 for the CNTRL Group ($p > 0.05$). Five-minute APGAR was 9.1 ± 0.3 for the MG Group, 7.4 ± 0.9 for the CNTRL Group ($p > 0.05$).

Discussion

Magnesium pre-treatment in this group of patients resulted in a significant decrease in DBP prior to intubation and significantly better control of SBP after intubation as compared to the CNTRL Group.

TABLE: Comparison of Hemodynamic Changes and Magnesium Levels

	After Pre-Rx	After Intubation	At Delivery
SBP (torr)	-13.0 ± 7.5	-8.7 ± 6.8*	-35.1 ± 9.7
MG	- 4.3 ± 7.8	13.6 ± 6.6	-25.0 ± 17.4
CNTRL			
DBP (torr)			
MG	-24.3 ± 2.8*	-8.6 ± 5.4	-19.3 ± 7.2
CNTRL	- 1.4 ± 0.9	12.1 ± 9.4	- 9.3 ± 15.2
Pulse (min^{-1})			
MG	8.7 ± 4.4*	8.3 ± 5.6	- 1.9 ± 7.3
CNTRL	- 4.0 ± 3.2	1.7 ± 11.5	9.1 ± 12.2
MG (mmol/l)			
MG	1.27 ± 0.31*	2.74 ± 0.3*	2.25 ± 0.22*
CNTRL	0.97 ± 0.16	1.07 ± 0.19*	0.93 ± 0.11

*Significant difference between groups at $p < 0.05$.

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Title: TREATMENT OF CITRATE-INDUCED HYPOCALCEMIA IN DOGS: COMPARATIVE RESPONSE TO CALCIUM CHLORIDE AND CALCIUM GLUCONATE

Authors: CJ Cote', M.D., LJ Drop, M.D., Ph.D., and AL Daniels, B.A.

Affiliation: From the Anesthesia Services of Massachusetts General Hospital and Shriners Burns Institute, and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts 02114

INTRODUCTION. Ionized hypocalcemia and resultant hemodynamic depression may occur during rapid transfusion of citrated blood products. Children may be at particular risk, since a unit of blood product represents a larger fraction of their blood volume. We therefore undertook an animal study to compare the efficacy of two calcium salts, calcium chloride ($CaCl_2$) and calcium gluconate (CaGlu), in treating citrate-induced hypocalcemia.

METHODS. Six conditioned mongrel dogs, 28-36 kg, were anesthetized with i.v. thiopental (15-20 mg/kg) followed by halothane in oxygen. Controlled ventilation maintained normal acid-base status, and measured end-tidal halothane assured a stable anesthetic depth. Thermodilution cardiac output (CO) and arterial, central venous, pulmonary artery and wedge (PCWP) pressures were measured. Each animal was studied on 4 separate days and received 3 doses of sodium citrate (CPD Formula A USP, Fenwal) equivalent to 0.5, 1.0, and 1.5 ml/kg/min fresh frozen plasma for 5 min. Either no calcium (controls) or calcium ($CaCl_2$: 4, 8, or 12 mg/kg, or CaGlu: 14, 28, or 42 mg/kg) was administered 1 min prior to citrate infusion.

RESULTS. Sodium citrate produced significant, dose-related reductions in MAP, [Ca++], and systemic vascular resistance (SVR), and increases in PCWP and HR (Table, Figure). As expected, SVR decreased in all dogs at all doses of citrate except those with near cardiac arrest. CO increased at the two lower doses of citrate but tended to decrease at the high dose (P = NS). Pre-treatment with either $CaCl_2$ or CaGlu attenuated, but did not completely eliminate, these changes at all doses of citrate. The high and medium doses of either calcium salt completely blocked clinically important cardiovascular effects of all doses of citrate, but did not prevent hypocalcemia at the higher doses of citrate. The lower doses of calcium were ineffective in preventing the cardiovascular effects of citrate. No significant cardiac dysrhythmias were observed following calcium. One dog suffered irreversible cardiac arrest during infusion of the highest citrate dose ([Ca++] = 0.19 mM).

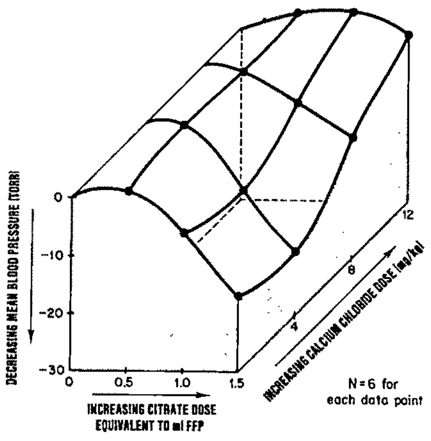
CONCLUSIONS. (1) Pre-treatment with calcium salts attenuates the effects of citrate-induced hypocalcemia; this is dependent upon the dose of calcium vs. the dose of citrate. Both calcium salts are equally effective when administered in equipotent doses, i.e., the ratio of $CaCl_2$ to CaGlu is 1:3. (2) Citrate-induced hypocalcemia depresses left ventricular function as indicated by a lowering of CO despite a significant rise in PCWP. (3) MAP is reduced by changes in both SVR and cardiac function.

TABLE

		HR (b/min)		MAP (mmHg)		CO (L/min)		SVR (R units)		PCWP (mmHg)		$[Ca^{++}]$ (mM)	
		Time after Infusion (min)											
		0	5	0	5	0	5	0	5	0	5	0	5
	■ CPD Alone:	99	114^*	80	62^*	3.4	2.8	23	23	5.6	7.4^*	1.29	0.58^*
Pre-Treatment	CPD + $CaCl_2$ (a)	103	126^*	80	79†	3.8	4.2	21	18	5.7	7.3^*	1.31	0.86^*†
	CPD + CaGlu (b)	101	122^*	86	88†	3.6	4.4^*†	25	20^*	5.8	7.5	1.43	0.97^*†

■ CPD equivalent to 1.5 ml/kg/min FFP
* $P < 0.05$ vs. baseline; † $P < 0.05$ vs. CPD alone
(a) = 12 mg/kg; (b) = 42 mg/kg

FIGURE



Title: CARDIOTOXICITY OF LOCAL ANESTHETICS DURING LATE PREGNANCY

Authors: JT Crandell, M.D., DM Kotelko, M.D., F.R.C.P.(C)

Affiliation: Department of Anaesthesia, University Hospital, University of Saskatchewan,
Saskatoon, Saskatchewan, Canada

Introduction. Emerging case reports indicate that the adverse effects of accidental iv bupivacaine are exaggerated during pregnancy possibly accounting for the greater majority of bupivacaine-related deaths occuring in obstetrical anesthesia. Although some animal studies have now verified the potent cardio-depressant and arrhythmogenic properties of bupivacaine, [1,2] only one investigation involved pregnant amimals [3]. Using a maternal-fetal sheep preparation, we investigated maternal cardiovascular effects and fetal outcomes after iv bolus injections of lidocaine, mepivacaine or bupivacaine.

Methods. Nineteen pregnant ewes near term and 1-3 yrs of age, had preparatory surgery while anesthetized with O_2 and halothane. Polyvinyl catheters were inserted into a femoral artery for continuous recording of BP, into a femoral vein for drug injection, into a carotid artery for blood sampling, and into an internal jugular vein for iv fluids. A pacing electrode was placed via an internal jugular vein into the right ventricle to record intracardiac ECG. A mid-line abdominal incision was made and the uterus was exposed. Through a small hysterotomy incision the fetal hind limbs were extracted. Polyvinyl catheters were placed bilaterally in the femoral arteries. The fetal limbs were then placed back and the uterus and abdominal incisions were closed.

To establish a sensory level in a 70 kg pregnant patient undergoing epidural anesthesia the required dose is approximately 20ml of 2.0% lidocaine (5.7 mg/kg), 20 ml 2.0% mepivacaine (5.7 mg/kg), or 20 ml 0.75% bupivacaine (2.1 mg/kg). Therefore, our study animals received amounts of lidocaine, mepivacaine or bupivacaine injected intravenously on a mg/kg basis over 10s ("low-dose") that would ordinarily be used in humans. To exaggerate cardiac effects, we gave some animals twice this amount ("high-dose"). The sequence of injection of local anesthetic was determined randomly, and given on separate days.

After a 24-hr recovery period, healthy ewes and fetuses were studied. Baseline values for cardiovascular variables, arterial blood gas and acid-base status were determined during a 30-min control period. The animals were awake and lying quietly, breathing room air or O_2-enriched air to ensure normal resting PaO_2 (60-100 mm Hg). Surface and intracardiac ECG's maternal systemic BP and fetal systemic BP were recorded continuously on a polygraph. To analyze arterial blood gases, acid-base status and drug concentrations, we obtained maternal blood samples at 1, 2, 3, 4, 5, 10, 15, 20 and 30 minutes and fetal blood samples 3, 5, 10, and 20 minutes after the iv injection of local anesthetic. Serum drug concentrations were determined by chromatographic methods (GLC & HPLC). 90 seconds after injection of local anesthetic, 100% O_2 was administered. Thiopental, 1.0 mg/kg iv was given to terminate seizures; other cardiotonic drugs were given as necessary for resuscitation.

We compared data using analysis of variance and paired student's tests when comparing the groups. The incidence of arrhythmias was compared using the chi^2 method. A $p < 0.05$ was considered statistically significant.

Results. As shown in the Table, equipotent boluses of iv lidocaine or mepivacaine were well tolerated by mother and fetus. In contrast, all animals receiving "low-dose" iv boluses of bupivacaine developed life-threatening ventricular arrhythmias. After iv boluses of "high-dose" bupivacaine, all ewes died despite aggressive CPR and pharmacologic therapy.

Fetal/maternal drug ratios were similar at 3 min. in all groups (.62 to .68) except the high-dose bupivacaine group (.45). At 3 min after iv injection of local anesthetic, fetal paO_2 decreased an average of 25% from control, whereas in the high-dose bupivacaine group, it decreased 62% from control. Fetal paO_2 was normal or above-normal in all groups 10 min after injection of local anesthetic except in the high-dose bupivacaine group where it remained 85% below control. Fetal heart rate (FHR) changes were most marked after high-dose bupivacaine injection, showing a signficantly greater fall in FHR in this group at 2 min. By 5 min. post-injection, all fetuses were alive but with FHRs 50% of control values. No fetus survived to 10 min despite vigourous maternal resuscitation attempts.

Table.

	Lidocaine		Mepivacaine		Bupivacaine	
Changes on ECG	L(n=5)	H(n=5)	L(n=5)	H(n=5)	L(n=5)	H(n=5)
Ventri tachy	0	0	0	0	4	2
Multiform PVC's	0	0	0	0	3	2
Widened QRS	0	0	0	0	4	5
Ventri fibrill	0	0	0	0	0	3
Death	0	0	0	0	1	5

Low dose = L, High dose = H

Conclusions. In normoxic, normocarbic pregnant ewes near term: (1) Equipotent boluses of iv lidocaine or mepivacaine produced benign cardiovascular effects in mother and fetus, (2) Bupivacaine boluses iv resulted in life-threatening maternal cardiac arrhythmias and after high-dose injection maternal cardiovascular collapse, and (3) Lidocaine, mepivacaine, and bupivacaine all readily crossed the placenta after iv bolus injection. Significant metabolic and hemodynamic changes occurred in the fetuses of the high-dose bupivacaine group despite vigorous resuscitation of the mother.

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Title: TRANSPLACENTAL TRANSFER OF NALBUPHINE IN PATIENTS UNDERGOING CESAREAN SECTION

Authors: ZP Dadabhoy, M.D., DP Tapia, M.D., and EK Zsigmond, M.D.

Affiliation: Department of Anesthesiology, University of Illinois College of Medicine, Chicago, Illinois

Introduction. Balanced anesthesia utilizing thiopental, ketamine, or thiopental supplemented with ketamine and $N_2O:O_2$ followed by intubation with the aid of succinylcholine have been safely used in patients undergoing Cesarean section. As long as the analgesic induced respiratory depression is properly reversed by the administration of naloxone to the mother, into the cord or to the neonate, the APGAR scores are not depressed and the fate of the neonate is not compromised by the administration of an analgesic. In the past, meperidine and fentanyl were primarily the agents used for supplementation of obstetric anesthesia with rapid transplacental transfer for all of these agents. A recently introduced agonist-antagonist, nalbuphine offers a safer alternative to anesthesia for Cesarean section, since it causes little respiratory or circulatory depression. Its transplacental transfer, however, has not been determined as yet. Therefore this study was undertaken.

Methods. Following approval of the Institutional Review Board, eight patients who gave valid written consent were studied. Their mean age ± S.D. was 26.6±5.5 years, mean weight ± S.D. was 77.3±23.7 kg, height was 163.1±7.1 cm. They were premedicated with 0.2 mg glycopyrrolate i.m. and 30 ml of 0.3 M sodium citrate p.o. 30-45 minutes before induction with a mean dose ± S.D. of 3.5± 0.8 mg/kg thiopental. They were intubated following 3.0 mg d-tubocurarine pretreatment and 1.5 mg/kg succinylcholine i.v., with cricoid pressure. After the confirmation of correct placement of the endotracheal tube, nalbuphine, 0.21±0.05 mg/kg diluted in 10 ml saline was injected over 30 seconds. The time to delivery after the injection of nalbuphine varied from 2 to 10 minutes with a mean of 5.6 minutes. APGAR scores were taken at 1 and 5 minutes. Blood samples were taken from the mother's peripheral vein and the cord of the neonate and blood levels were determined by gas-chromatography mass-spectrophotometry. Blood pressure and pulse rate were intermittently determined by a non-invasive trend recorder.

Results. As Table 1 shows, the mean blood level of nalbuphine in the parturient was 64.1±20.8 ng/ml, while in the neonate the blood level was significantly higher than in the parturient, a mean ± S.D. of 89.3±19.3 ng/ml. Therefore the transplacental ratio was found to be 1.4/1. This represented very rapid transplacental transfer of nalbuphine, more rapid than that of either meperidine or fentanyl. Delivery occurred within a mean of 5.6±2.3 minutes after the administration of 0.21±0.05 mg/kg of nalbuphine. There was a linear correlation between injected dose and either maternal or neonatal blood levels. Despite this very rapid transplacental transfer of nalbuphine and high blood levels in the neonate, the mean APGAR scores were: 6.6±2.5 at 1 minute and 8.5±2.1 at 1 and 5 minutes. No correlation was observed between the time interval from injection to the delivery and neonatal nalbuphine blood levels, nor was any correlation found between neonatal blood levels and APGAR scores. No significant hemodynamic changes occurred after nalbuphine administration as shown in Figure 1.

Discussion. 1) The transplacental transfer of nalbuphine is rapid, the neonatal/maternal ratio is 1.4/1. 2) Despite this rapid transplacental transfer of nalbuphine, APGAR scores at 5 minutes were acceptable. 3) No correlation was observed between neonatal blood levels and APGAR scores. 4) Based on the lack of the cardio-circulatory changes observed in the mother and the acceptable APGAR scores observed in this small patient population, it is likely that nalbuphine will be an acceptable analgesic component of intravenous anesthesia for Cesarean section. Further studies on the cardio-circulatory effects of nalbuphine in neonates are warranted.

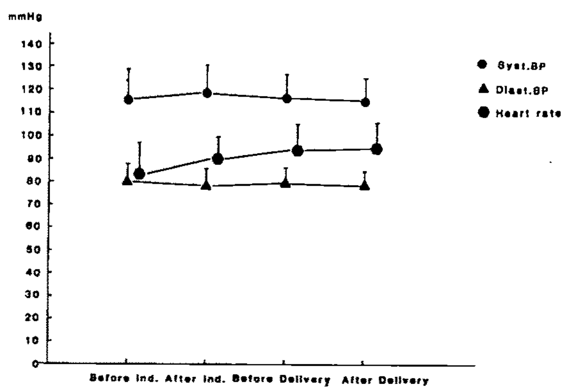
Table 1

NALBUPHINE BLOOD LEVELS IN MOTHER AND NEONATES

	Mother ng/ml	Neonate ng/ml
#1	102.05	64.50
#2	79.11	124.37
#3	28.56	96.99
#4	62.92	72.52
#5	65.81	93.29
#6	58.63	85.36
#7	59.84	75.08
#8	55.88	102.73
Mean	64.1	89.35
S.D.	20.8	±19.27

Figure 1

HEMODYNAMIC CHANGES DURING THIOPENTHAL-NALBUPHINE ANESTHESIA FOR CESAREAN SECTION



Title: A COMPARISON OF AUTOMATED OSCILLOMETRIC AND CATHETER-TRANSDUCER MEASUREMENTS OF ARTERIAL PRESSURE

Author: R.F. Davis, M.D.

Affiliation: Department of Anesthesiology, University of Florida College of Medicine, Gainesville, FL 32610

Introduction. A variety of devices are available that measure arterial pressure noninvasively and automatically by using either oscillometric or auscultatory techniques. This investigation was designed to compare arterial pressure (systolic, diastolic, and mean) measured oscillometrically by one such device (Vitalcheck®, IVAC, Corp.) with that measured invasively by arterial catheterization, with both devices used at the same time and applied to the same arm.

Materials and Methods. Fifty patients who required invasive (catheter-transducer) measurement of arterial pressure during surgical operations and who were anesthetized by this author were selected for study. Catheter-transducer measurement of arterial pressure was accomplished with a 2-in, 20-ga, nontapered, Teflon® catheter placed percutaneously into the radial artery and connected in sequence to a 4-foot section of rigid polyethylene tubing (Cobe, Inc.), a continuous infusion device (Intraflo®, Sorenson, Inc.), and a Hewlett-Packard (Model 1290) or a Bentley (Model 800) transducer. The fundamental frequency response and damping coefficient characteristics of the arterial catheter, connecting tubing, and transducer as a unit were determined by the "snap" test as described by Gardner (1). Arterial pressure waveforms were continuously recorded on a Hewlett-Packard strip chart recorder driven at a paper speed of 25 mm/min. Mean values of the transduced pressure waveform were calculated from the strip chart data by the formula: mean = diastolic + [1/3 (systolic − diastolic)]. Transducers were appropriately zeroed and statically calibrated with a mercury column before pressure recording. Arterial pressure was assessed noninvasively by the oscillometer, with an appropriately sized cuff placed around the upper arm on the extremity in which the radial artery catheter was inserted. Digital data from the oscillometer were compared with averaged values obtained from the catheter-transducer system over the 10-s period immediately before inflation and immediately after deflation of the oscillometer cuff. By this method arterial pressure measurements from the two techniques were as close to simultaneous as possible. If the systolic pressure value obtained from the catheter-transducer immediately before cuff inflation differed from the corresponding value obtained immediately after cuff deflation by more than 10%, that set of data (systolic and diastolic, catheter-transducer and oscillometer) was excluded from the analysis. Oscillometric and catheter-transducer data were compared by linear regression analysis. Differences between pairs of the two measurement techniques were compared by Student's t test.

Results. The 50 patients ranged in age from 14 to 75 years and the surgical procedures included cardiac, neurologic, and general surgical procedures. A total of 399 pairs of data were obtained, of which 14 were excluded from analysis because of variability in the catheter-transducer pressure measurements as described. Thus, comparisons are based on analyses of 385 pairs of data from 50 patients. Data from the "snap" test of the catheter-transducer system revealed a fundamental frequency response of 23.7 ± 2.6 Hz with a damping coefficient of 0.26 ± 0.02. The regression relationships for all 385 pairs of data are: systolic: Vitalcheck® = 0.92 (catheter-transducer) + 3.52, $r = 0.91$; diastolic: Vitalcheck® = 0.92 (catheter-transducer) + 1.34, $r = 0.76$; and mean: Vitalcheck® = 0.96 (catheter-transducer) + 0.68, $r = 0.84$. The differences between measurement techniques (catheter-transducer minus oscillometer) were: systolic: 5.2 ± 0.4 mmHg, diastolic: 3.7 ± 0.5 mmHg; and mean: 2.3 ± 0.4 mmHg. These values corresponded to percent differences of 4.5 ± 0.3, 5.5 ± 0.7, and 2.7 ± 0.5, respectively. Differences between the two techniques, whether expressed in absolute or in percent difference, were statistically significant for all three pressures ($P < 0.01$).

Discussion. The principal finding of this investigation is the close linear correlation between oscillometric and invasive determinations of systolic, diastolic, and mean arterial pressures. Among individual regression analyses, the strongest correlation was for systolic pressure and the weakest for diastolic pressure. This observation is consistent with the physical principles underlying the oscillometric pressure measurement technique, where signal strength for systolic and mean pressures is substantially stronger than that for diastolic pressure (2). Despite the overall strong correlation between the two techniques, there was a small but statistically significantly lower value obtained with the oscillometer than with the catheter-transducer for systolic, diastolic, and mean pressure values.

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Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF ATRACURIUM UNDER ISOFLURANE ANESTHESIA IN NORMAL AND ANEPHRIC PATIENTS

Authors: Frederic M. de Bros, M.D., A. Lai, Ph.D., R. Scott, M.D., J. de Bros, CRNA, A.G. Batson, B.S., N. Goudsouzian, M.D., H.H. Ali, M.D., J.J. Savarese, M.D.

Affiliation: Department of Anesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA and Wellcome Laboratories, Burroughs Wellcome Company, Research Triangle Park, NC

Introduction: Atracurium besylate (Tracrium^{R}) is a relatively new nondepolarizing muscle relaxant with an intermediate duration of action. Its novelty is a unique metabolic pathway. Atracurium is degraded via two nonoxidative processes (Hofmann elimination and ester hydrolysis), which generally take place outside the liver and kidney. In this study, we evaluated the pharmacokinetics and pharmacodynamics of atracurium during isoflurane anesthesia to (a) confirm the previous data independently[1,2] and (b) to investigate a possible effect of isoflurane on these parameters.

Methods: Sixteen patients (8 normal and 8 anephric) were studied after having given institutionally approved informed consent. Renal failure patients were dialysed within 24 hours prior to surgery. Premedication was 5-10 mg Diazepam p.o. Anesthesia was induced with 4 mg/kg sodium thiopental and intubation was performed under isoflurane, N_2O-O_2 anesthesia without the use of muscle relaxants. Anesthesia was maintained with 0.75 to 2% isoflurane in 60% N_2O and 40% O_2. Temperature was kept within physiological range. Neuromuscular function was measured by recording the force of thumb adduction with a Grass FT10 transducer and recording the single twitch delivered via a Grass S88 stimulator through needle electrodes to the ulnar nerve at the wrist.

After stabilization of vital signs, Atracurium 0.5 mg/kg was injected over a 20 second period. Blood samples for the determination of plasma levels of atracurium were drawn at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90 and 120 minutes. Samples were handled and analysed according to a modified method[3] of Neill.[4] Data were fitted to a two compartment pharmacokinetic equation. We calculated the volume of distribution (Vdβ) the plasma half life ($t_{1/2}\beta$) and plasma clearance (Cl). Onset, duration and recovery time were measured from the twitch recordings. Data were compared by t-test and significance was assumed at the $p < 0.05$ level.

Results: The table shows data on 6 normal and 5 anephric patients. A full set of results will be presented at the meeting. The figure shows plasma concentrations of atracurium after a 0.5 mg/kg bolus injection to a representative anephric patient.

Discussion: Plasma half life, volume of distribution and clearance in the renal failure group were similar to the values of normal patients. In this set of data, differences are not statistically significant. The virtually identical plasma clearance values in both groups are the basis for our conclusions.

Conclusion: Anephric patients distribute and eliminate atracurium much like normal patients. These results confirm earlier findings. Further, in comparison to a previous study[2], we found that duration of neuromuscular blockade and recovery times were slightly prolonged (NS) after the administration of an equivalent dose of atracurium. This is probably due to the effect of the volatile anesthetic agent.

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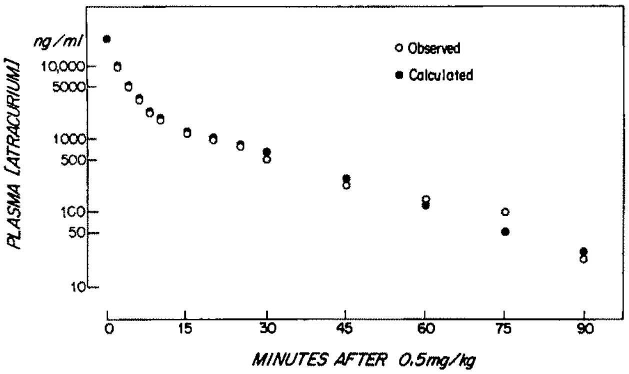
Parameter	Normal Patients n=6	Renal Failure n=5
Vdβ (ml/kg)	140±37	166±40
$t1/2\beta$ (min)	17±2	18±3
Cl (ml/kg/min)	5.8±2.0	6.3±2
Onset (min) (inj→max block)	2.0±0.9	3.0±0.9
Duration I (min) (inj→25% recovery)	53±14	45±15
Duration II (min) (inj→95% recovery)	85±18	72±20
Recovery time (min) (25→75% twitch height)	18±12	17±10

All values mean + SD



Title: NEUROENDOCRINE AND HEMODYNAMIC RESPONSES TO INDUCED HYPOTENSION DURING TOTAL HIP ARTHROPLASTY

Authors: J Ebert, D.O., C Malloy, CRNA, P Laborde, CRNA, J Proctor, EL Bradley, Jr., Ph.D., and K Niemann, M.D.
Affiliation: Departments of Anesthesiology, Biostatistics, and Orthopaedics, The University of Alabama in Birmingham, Birmingham, Alabama 35294

Introduction. It is well established that plasma levels of cortisol are elevated during surgical procedures as well as during hypovolemic hypotension. The purpose of this study was to assess the neuroendocrine response to vasodilator-induced hypotension in patients undergoing total hip arthroplasty using two different anesthetic techniques.

Methods. Twenty-four patients (ASA status I-III) undergoing total hip arthroplasty were included in this study. Institutional Review Board approval and informed consent from each patient were obtained. Preoperative medication included diazepam, 10 mg and cimetidine, 300 mg orally. Anesthesia was induced with thiopental, 2-5 mg · kg^{-1} I.V., and endotracheal intubation facilitated by succinylcholine, 1 mg · kg^{-1} I.V. Lidocaine, 2 mg · kg^{-1}, was sprayed topically prior to intubation. Metocurine was used for subsequent muscle relaxation. The end-expired concentrations of enflurane and nitrous oxide were measured with a Perkin-Elmer mass spectrometer. Radial arterial and right internal jugular venous catheters were inserted percutaneously for blood sampling and the measurement of arterial and central venous pressure, respectively. Four groups of 6 patients each were studied: group I received nitrous oxide, 0.65 MAC, plus intravenous fentanyl, 15 μg · kg^{-1} initially, followed by one-quarter of this dose every 30 minutes for the first hour, followed by one-eighth of the initial dose every 30 minutes thereafter. This method of administration of fentanyl was developed using a pharmacokinetic model of fentanyl based on studies by McClain and Hug.[1] This dosage schedule would assure a relatively constant plasma level of the drug. Group II was the same as group I with the addition of sodium nitroprusside intraoperatively, resulting in a 30% decrease in the mean blood pressure from the control level. Group III was given nitrous oxide, 0.65% plus enflurane, 1 MAC (1.7% end-tidal) and group IV was treated as group III, with the addition of sodium nitroprusside to induce the same degree of hypotension as in group II. In all groups, nonglucose-containing crystalloids and blood were administered to maintain CVP and hematocrit values. Hemodynamic variables and blood samples for catecholamine, cortisol, and glucose measurements were taken at eleven consecutive stages. The data from the day prior to surgery (control), the mean of 5 intraoperative values (intra), and 2 hours after the completion of surgery (post) are presented here. Cortisol concentrations were determined by radioimmunoassay, and glucose by the glucose oxidase method. Statistical significance ($P < 0.05$) was determined by two factor analysis of variance.

Results. There were no significant differences in the control measurements between groups. Intraoperative cortisol and glucose levels were elevated in the hypotensive groups, while they were increased in all groups postoperatively. Intraoperative cortisol and glucose levels were higher in the hypotensive fentanyl group compared to the normotensive counterparts. In the hypotensive fentanyl patients, the intraoperative cortisol levels were lower than in the hypotensive enflurane group, but higher than in the normotensive fentanyl patients. Intraoperative glucose concentrations were also higher in the hypotensive fentanyl patients than in the normotensive counterparts, while postoperatively the glucose levels were higher in the hypotensive fentanyl patients than in the corresponding enflurane patients.

Discussion. Sodium nitroprusside-induced hypotension was accompanied by glucose and cortisol concentrations greater than those associated with normotension, when the same anesthetic techniques were employed. This may be interpreted as an additional stress response beyond that associated with surgery. While fentanyl anesthesia in the doses employed here blunted the neuroendocrine response to surgery better than enflurane anesthesia, enflurane was superior to fentanyl in preventing this additional response associated with induced hypotension. As an added benefit, enflurane was superior to fentanyl in altering the increased heart rate associated with nitroprusside-induced hypotension.

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Hemodynamic and Metabolic Values in Patients Undergoing Total Hip Arthroplasty (Mean ± SEM)

			CONT	INTRA	POST
I	Fent Norm	HR	77.6±4.2	57.3±2.8$^{*,+}$	83.1±5.6
		MBP	92.8±3.7	89.3±3.5	95.8±4.3
		Cort	10.88±1.32	12.84±2.79^{+}	28.22±3.47*
		Gluc	89.4±7.9	102.6±8.7	137.6±17.2*
II	Fent Hypo	HR	79.3±3.8	89.1±7.2^{+}	85.5±8.9
		MBP	88.8±2.2	65.8±2.7$^{+,*}$	83.8±2.0
		Cort	12.21±1.44	21.06±2.05$^{*,+,\ddagger}$	37.13±3.00$^{*,+}$
		Gluc	109.3±5.5	156.3±16.0$^{*,+}$	198.8±22.8$^{*,+,\ddagger}$
III	Enfl Norm	HR	81.1±5.3	90.8±5.7*	85.5±6.0
		MBP	101.8±4.7	84.8±7.1*	101.0±4.9
		Cort	15.83±2.89	23.46±2.52	24.86±2.76*
		Gluc	93.8±4.7	119.1±6.9*	136.5±13.0*
IV	Enfl Hypo	HR	78.1±3.8	75.3±4.5	73.3±3.5
		MBP	101.0±5.2	72.3±4.0$^{*,+}$	84.1±8.0^{+}
		Cort	16.18±2.90	29.74±1.53*	31.02±1.40*
		Gluc	109.3±8.3	144.5±2.7*	141.1±6.4*

Group I = nitrous oxide 0.65 MAC + fentanyl 15 μg · kg^{-1} I.V. + maintenance doses; Group II = nitrous oxide 0.65 MAC + fentanyl 15 μg · kg^{-1} I.V. + maintenance doses + SNP-induced hypotension; Group III = nitrous oxide + enflurane 1.6 MAC; Group IV = nitrous oxide + enflurane 1.6 MAC + SNP-induced hypotension. Cont = control; intra = intraoperative; post = 2 hours postoperative. HR = heart rate in beats · min^{-1}; MBP = mean blood pressure in mm Hg; Cort = cortisol concentration in ng · ml^{-1}; gluc = glucose concentration in mg · dl^{-1}.

* = $p < 0.05$ vs. control in same group
+ = $p < 0.05$ vs. normotensive group w/same anesthetic
‡ = $p < 0.05$ vs. enflurane group w/same condition (MBP)

Title: THE LETHAL DOSE OF INTRAVENOUS BUPIVACAINE WITH AND WITHOUT EPINEPHRINE IN RABBITS

Authors: EA Eisler, M.D., DA Shapiro, M.D., SM Shnider, M.D., SH Halpern, M.D., G Levinson, M.D., MA Rosen, M.D., J Johnson and MJ Jones, B.A.

Affiliation: Departments of Anesthesia, University of California San Francisco, CA 94143 and Letterman Army Medical Center, San Francisco, CA 94129

Introduction: Bupivacaine has been reported to cause life-threatening arrhythmias in normal animals[1] and cardiovascular collapse and death in hypoxic and acidotic animals.[2] Several case reports of accidental intravenous injection of bupivacaine suggest that bupivacaine can also be cardiotoxic in humans.[3] In most of these clinical reports as well as the animal studies, bupivacaine without epinephrine was used. Moore and Scurlock[4] have postulated that the use of epinephrine-containing solutions may prevent the myocardial depression which occurs with accidental intravenous injection of bupivacaine. We investigated this hypothesis by constructing dose response curves for the lethal dose of bupivacaine solutions with and without epinephrine and determined the LD_{50} for each solution. We studied unanesthetized rabbits rendered acidotic and hypoxic to simulate the acidosis that often occurs during local anesthetic-induced seizures in humans.

Methods: Under halothane/oxygen anesthesia, catheters were inserted into femoral arteries and veins of 70 rabbits. After recovery from preparatory surgery, animals were given a mixture of air, CO_2, and nitrogen to breathe until arterial pH was between 7.12 and 7.18 and PaO_2 was 10 to 20 torr below control. Rabbits then received an intravenous injection of either 0.5% bupivacaine plain or 0.5% bupivacaine with epinephrine 1:200,000 over 10 sec. Five animals were studied at each of a variety of doses ranging from 1.0 to 2.8 mg/kg. Continuous EKG and arterial pressure tracings were monitored for the first 5 minutes following injection. Dose response curves were constructed by plotting mortality (%) against drug dose by the method of Litchfield and Wilcoxon.[5]

Results: The LD_{50}'s of a bolus dose of bupivacaine with and without epinephrine were almost identical, i.e., 1.56 mg/kg with epinephrine and 1.62 without epinephrine (figure). The slope of the curve for plain bupivacaine was 1.35 and for bupivacaine with epinephrine, 1.18. These were not significantly different.

Discussion: When plotting dose of bupivacaine against mortality in acidotic rabbits, a very steep curve is produced (figure). This is not modified by adding epinephrine to the solution nor is the LD_{50} changed by epinephrine. We cannot predict the effect of larger doses of epinephrine, but would note that larger doses go beyond those commonly used. We conclude that the addition of epinephrine 1:200,000 does not protect against the cardiotoxicity of bupivacaine in acidotic rabbits.

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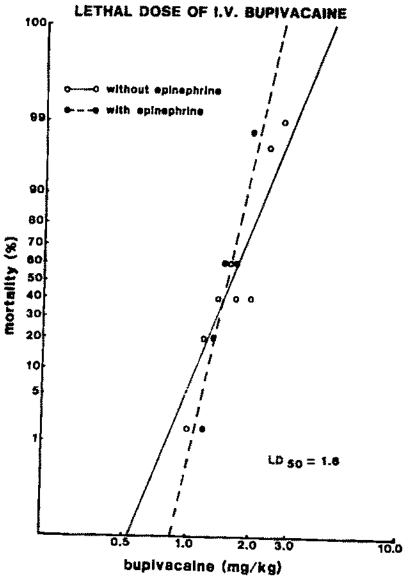

Title: BETA ENDORPHIN IN INDUCED HYPOTENSION: RELATION TO SYMPATHOADRENAL AND CARDIOVASCULAR RESPONSES

Authors: N.R. Fahmy, M.D., D. Carr, M.D., P. Mihelakos, M.D., D.G. Lappas, M.D.
Affiliation: Anesthesia Service and Endocrine Unit at Massachusetts General Hospital and the Departments of Anaesthesia and Medicine, Harvard Medical School, Boston, MA 02114

INTRODUCTION: Hypotension due to hypovolemia or endotoxin shock causes brisk elevations in plasma levels of immunoreactive β-endorphin (β-END).[1] No studies have yet described β-END levels during hypotension induced by vasodilation. This is the subject of the present report.

METHODS: Studies were conducted on seven consenting ASA Class I or II patients who received oral diazepam, 0.1 mg/kg, for premedication. Thiopental (5 mg/kg) was used for induction followed by succinylcholine (1 mg/kg) for intubation. Anesthesia was maintained with halothane (1%), N_2O-O_2 (3:2 l/min), and curare (0.4 mg/kg). Induced hypotension (IH) with a mixture of nitroprusside (25 mg) and trimethaphan (250 mg) in 5% dextrose solution was begun before surgical incision. Circulatory variables and arterial blood samples were obtained before and one hour after induction of anesthesia. After the second blood sample, IH commenced and surgical incision followed 10 minutes later. Measurements were repeated 15,30,45, and 60 minutes after IH began. Two final measurements were obtained just before termination of hypotension and 15 minutes later. Blood was analyzed for 1) immunoreactive β-endorphin and lipotropin (RIA)[1]; 2) plasma renin activity (RIA); 3) plasma catecholamines (radioenzymatic assay); 4) plasma aldosterone (RIA); and 5) gases and electrolytes. Data were examined by analysis of variance and Student's t test.

RESULTS: Administration of the hypotensive mixture produced a smooth decrease in pressure. Mean arterial pressure decreased from 75 ± 2.4 to between 51 and 55 mm Hg during hypotension; no rebound increase occurred following discontinuation of infusion. Heart rate and cardiac output did not change significantly. β-END levels increased steadily during hypotension from 30.9 pg/ml (before hypotension) to 38, 44.7, 64.5, 77.1 pg/ml (every 15 min for 1 hour); they were 129 pg/ml at end of hypotension. PRA, catecholamines, and aldosterone, likewise, showed significant increases during hypotension. The mean doses of nitroprusside and trimethaphan were 0.3 mg/kg and 3 mg/kg, respectively, with a mean duration of hypotension of 241 min.

DISCUSSION: The present study demonstrates that plasma β-END rises gradually during IH, in contrast to the rapid and marked (10 times) elevations in other types of hypotension. Our results also show that plasma β-END changes in conjunction with plasma renin activity and aldosterone in response to IH, and that rises in these three hormones lag the increases in catecholamines. Confirming others,[2] we did not observe changes in β-END levels during anesthetic induction and surgical incision.

CONCLUSIONS:

1. The slow rise of β-END during IH and its abrupt drop (to 78.7 pg/ml) after termination of IH suggests that when cardiac output is held constant, factors besides surgical stress or vasodilation contribute to β-END release.
2. Our failure to confirm prompt rises in β-END during surgery as reported by DuBois et al[3] may reflect differences in anesthetic techniques, surgical procedures, or assay methods. Hemodynamic status and surgical effects on hormone levels were not specified.[3]
3. Activation of opioid pathways during IH may augment the hypotensive effects[4] of trimethaphan and nitroprusside, and help reduce MAC of inhalational anesthetics.
4. Trimethaphan or nitroprusside may influence β-END responses to surgical stress and IH.[5]
5. Further studies of these hormonal responses to stress may help elucidate reciprocal interactions of opioid peptides and catecholamines.[6]

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TITLE: EPIDURAL MORPHINE FOR POSTOPERATIVE ANALGESIA IN PEDIATRIC PATIENTS

AUTHORS: D. A. Finholt, M.D., J. A. Stirt, M.D., C. A. DiFazio, M.D., Ph.D.

AFFILIATION: Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, VA 22908

Introduction. Previous studies have demonstrated the benefits of epidural narcotics for pain relief in adults (1,2). Little information exists on the use of epidural narcotics in the pediatric population. We report here our experience with epidural morphine for postoperative analgesia in children.

Methods. This evaluation received institutional approval and informed consent was obtained. Seven children, ages 10-17, received postoperative epidural morphine analgesia. Indications for choosing this technique were anticipated postoperative respiratory difficulty (obesity, cystic fibrosis) or previous severe emotional reactions to painful procedures (chronic diseases). Following induction of anesthesia and endotracheal intubation, epidural catheters were placed at the L2-3 interspace, using a 17g Tuohy needle and a loss of resistance technique. Luer lock adapters with bacteriostatic filters were attached to the free end of the catheters. Maintenance anesthesia consisted of epidural lidocaine 1½% combined with N_2O/O_2 anesthesia or general anesthesia with halothane/N_2O/O_2. Thirty to 45 minutes prior to the end of surgery, preservative-free morphine was injected through the epidural catheter, with doses calculated per cm of patient height. At the end of surgery, inhalation anesthesia was discontinued and the patients taken to the recovery room. Two hours following initial administration of epidural morphine the patients were asked if they were comfortable. If not, the initial dose of epidural morphine was repeated. Once the patients were comfortable, a naloxone infusion was begun at 10 µg/kg/hr. If unwanted side effects of morphine appeared, 1 µg/kg IV naloxone boluses were administered and the naloxone infusion rate was increased to 20 µg/kg/hr. Repeat doses of epidural morphine were administered when patients requested more pain relief. The catheters were removed 22-32 hours postoperatively.

Results. Results from all 7 patients are summarized in the table and the figure. The initial dose of morphine ranged from 24-31 µg/cm of patient height. Two patients required repeat doses of epidural morphine to become comfortable. Initial analgesia lasted a mean of 16 hours and subsequent doses gave analgesia for 14 hours. The dosing pattern was quite variable between patients (figure). No patient required systemic analgesia supplementation. Side effects were pruritus, nausea, urinary retention and drowsiness. All side effects except drowsiness were diminished or abolished by supplemental doses of IV naloxone and increases in the naloxone infusion rate. No patients had respiratory depression as measured by respiratory rate.

Discussion. This report demonstrates that postoperative analgesia with epidural morphine can be used successfully in pediatric patients. Although postoperative respiratory problems were anticipated in 4 of the 7 patients, none materialized. Another 3 patients had previous histories of emotional difficulties with hospitalization and painful procedures. We felt these patients in particular would benefit from epidural narcotic analgesia. Parents, patients, and nurses reported satisfaction and some surprise at the smooth postoperative courses. Drowsiness separate from respiratory depression has not been reported in adults as a side effect of epidural morphine administration. In spite of drowsiness, our patients maintained normal respiratory rates, were easily arousable and moved about their rooms without difficulty. Reasons for the drowsiness are not clear. It is possible these patients were simply comfortable and fatigued following the physical and emotional stress of major surgery. Another possible etiology is cephalad spread of morphine via the cerebrospinal fluid into the brain. The naloxone infusion may have prevented more significant signs of central nervous system depression. In summary, we report the successful use of postoperative epidural morphine analgesia in seven children. Drowsiness was an unexpected side effect but caused no major complications.

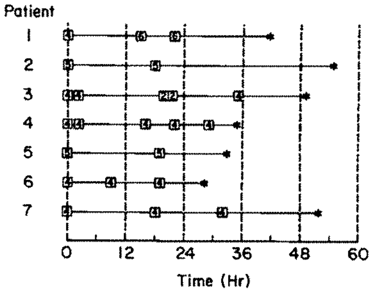
Table. Dose, Duration of Analgesia, and Side Effects of Epidural Morphine

Patient	Age (yr)	Weight (kg)	Height (cm)	Initial Morphine Dose (mg)	Initial Morphine Dose (µg/cm of height)	Duration of Initial Analgesia (hr)	Side Effects†
1	13	55	157	4	25	15	P, D
2	15	57	173	5	29	18	P, N, D
3	15	50	170	4	24*	18	P, U, D
4	13	40	163	4	25*	14	P
5	12	67	160	5	31	19	N
6	17	35	165	4	24	10	
7	10	30	147	4	27	18	D

*Repeat dose required for initial analgesia

†P = pruritis, N = nausea, U = urinary retention, D = drowsiness

Figure. Dosing pattern of epidural morphine



*First dose of systemic analgesia

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Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF VECURONIUM IN ANESTHETIZED INFANTS AND CHILDREN

Authors: D. M. Fisher, M.D., K. Castagnoli, B.A., and R. D. Miller, M.D.
Affiliation: Department of Anesthesia, University of California, San Francisco, California 94143

Introduction. Although the ED_{50} for vecuronium is similar for infants (16.5 µg/kg) and children (19.0 µg/kg) during N_2O-halothane anesthesia, duration of neuromuscular blockade after vecuronium (70 µg/kg) is markedly longer in infants (73 ± 27 min, mean ± SD) than in children (35 ± 6 min) (1). To determine whether this difference results from age-related changes in metabolism, distribution, or sensitivity, we determined the pharmacokinetics and pharmacodynamics of vecuronium.

Methods. We obtained approval from our committee on human research and informed consent to study 5 infants (3-11 mo) and 5 children (1-5 yr). Anesthesia was maintained with an end-tidal halothane concentration equivalent to 0.9 MAC (age-adjusted) and 70% N_2O. Ventilation was controlled to keep end-tidal PCO_2 at 30-40 mmHg; nasopharyngeal temperature was kept at 35-37°C.

The ulnar nerve was stimulated with single, supramaximal, 0.15-msec stimuli administered at 0.15 Hz; and the strength of contraction of the adductor pollicis was measured with a force transducer. We then administered vecuronium by iv infusion (2.5 µg/kg/min) until twitch tension was depressed 70-80%. Plasma samples, 0.5 ml each, were obtained for 4 hr.

Concentrations of vecuronium were determined using a mass spectrometric technique sensitive to 0.5 ng/ml, specific for unmetabolized parent compound, with a coefficient of variation ranging from 5-15%. Elimination half-life ($t_{1/2}\beta$) was determined by linear regression of the postdistribution log plasma concentration vs time. Total plasma clearance (Cl) and volume of distribution at steady-state (Vd_{ss}) were determined using noncompartmental techniques; mean residence time (MRT) was calculated as Vd_{ss}/Cl.

To determine pharmacodynamics, we fit the curve for plasma vecuronium concentration vs time for each patient to a 3-compartment pharmacokinetic model. Values for twitch tension were then fitted to the estimates of the kinetic parameters using an effect-compartment pharmacodynamic model. This permits estimation of the steady-state plasma concentration that results in 50% depression of twitch tension [$Cp_{ss(50)}$], the rate constant for equilibration between the central and effect compartments ($t_{1/2}k_{eo}$), and the exponent of the Hill equation (γ). We also calculated the product of Vd_{ss} and $Cp_{ss(50)}$, D(50). Mean values for the two groups were compared using Student's t-test for unpaired data. For all comparisons, $P < 0.05$ was considered statistically significant.

Results. Vd_{ss} and MRT were greater in infants (table). $t_{1/2}\beta$, Cl, $t_{1/2}k_{eo}$, γ, and D(50) did not change with age. $Cp_{ss(50)}$ was lower in infants.

Discussion. The longer duration of vecuronium-induced neuromuscular blockade for infants should be related to a slower decrease in the plasma concentration; plasma concentration would decrease more slowly because of age-related changes in Vd_{ss} or Cl. We expected changes in Vd_{ss} because distribution of muscle relaxants such as vecuronium is limited to extracellular fluid (ECF) whose volume decreases markedly during the first year of life. We also expected age-related changes in Cl since vecuronium appears to be eliminated by the liver. Despite the usual finding that hepatic activity is lower in infants than adults, we found that Cl of vecuronium did not change with age. The age-related changes in Vd_{ss} and lack of changes for Cl are similar to those for d-tubocurarine (dTc) (2).

The combination of a larger Vd_{ss} in infants and a lack of age-related changes in Cl results in a longer MRT, a finding consistent with the longer duration in infants. In contrast, age-related changes in $t_{1/2}\beta$ were not parallel to changes in duration of action: after a single dose of a muscle relaxant, recovery of neuromuscular function depends on distribution and elimination rather than on elimination alone.

The finding that $Cp_{ss(50)}$ changes with age is similar to the findings for dTc (2) and is consistent with the observation that newborns demonstrate posttetanic exhaustion at lower stimulation rates compared to adults. Since there are age-related changes in both Vd_{ss} and $Cp_{ss(50)}$, we calculated D(50), the quantity of vecuronium present at steady-state at 50% depression of twitch tension. D(50) did not change with age; thus, the age-related changes in Vd_{ss} and $Cp_{ss(50)}$ counterbalance each other. This result is consistent with our finding that ED_{50} for vecuronium does not change with age, and is similar to the findings for dTc (2).

In summary, the age-related changes in Vd_{ss} and $Cp_{ss(50)}$ counterbalance each other and resulted in values for D(50) that did not change with age. There were no age-related changes in Cl; thus, the MRT in infants results from a larger Vd_{ss}. The longer MRT in infants and the lack of age-related change in D(50) are consistent with findings that dose requirements are similar for infants and children but that duration of action and recovery time are longer in infants. In addition, these results are similar to the age-related changes for dTc.

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Table. Pharmacokinetic and Pharmacodynamic Data for Infants and Children (Mean ± SD)

	Infants	Children
N	5	5
$t_{1/2}\beta$ (min)	64.7 ± 30.2	41.0 ± 15.1
Cl (ml/kg/min)	5.6 ± 1.0	5.9 ± 2.4
Vd_{ss} (ml/kg)	357 ± 70	204 ± 116*
MRT (min)	66.3 ± 22.9	34.3 ± 8.0*
$Cp_{ss(50)}$ (ng/ml)	57.3 ± 17.7	109.8 ± 28.1*
$t_{1/2}k_{eo}$ (min)	3.9 ± 1.6	4.0 ± 0.6
γ	5.2 ± 1.4	6.0 ± 0.8
D(50) (µg/kg)	21.2 ± 9.9	19.0 ± 3.3

* Different from infants by Student's t test.

Title: MEAN BODY TEMPERATURE OF RECOVERY ROOM ADULTS

Authors: KE Fraulini, M.S.N., AC Borchardt, B.S.N., DC Randall Andrews, M.S.*,
and F Slaymaker, Ph.D.**
Affiliations: *Department of Operating Room and Surgical Nursing, Rush-Presbyterian-St.Luke's Medical
Center, Chicago, Illinois and **Loyola University of Chicago, Chicago, Illinois.

Introduction. While hypothermia ($T_{bc}<36^{\circ}C$) (2) is known to occur as a consequence of surgery and anesthesia, there are few studies which have determined incidence of hypothermia and hypothermia as a function of numerous clinical variables in adult recovery room (R.R.) patients. Hypothermia, if unrecognized, may represent a significant clinical risk during the early postoperative period. Examples are shivering, which increases oxygen demand by as much as 400-500%, increased minute ventilation with simultaneous increase in cardiac output, and prolonged plasma half-lives of parenterally administered drugs. Previous investigators collected core temperature measurements on 198 R.R. patients 17 years or older. Study results indicate that hypothermia occurs frequently in adults after surgery and anesthesia (60% of subjects had temperatures < 36°C on admission to the R.R.). Further, in spite of an average 82 minute R.R. stay, 13% of subjects were still hypothermic on discharge. (2) The present study was designed to determine mean body temperature of adult recovery room patients and to identify patients or patient groups who may be at increased risk of hypothermia.

Methods: Following Institutional Human Investigations Committee approval, data were accumulated prospectively on 312 adult R.R. patients. Adults (17 years or >) admitted to the R.R. were monitored for axillary temperature on admission and approximately every 15 minutes thereafter by staff R.N.'s. These nurses were instructed in the research protocol and reinstructed in placement of the temperature probe. Six FILAC F-1010 electronic thermometers were used in the study. Mean body temperature was defined as assessment of total body heat which takes into account the temperature of the central and peripheral tissues. Burton (1935) derived an equation for the mean body temperature using the mean skin temperature and the rectal temperature as a measure of core body temperature. Mean body temperature = (0.66 x rectal temperature) + (0.34 x mean skin temperature). (1) Descriptive statistics, repeated measures analysis of variance and regression analysis were used to examine the data.

Results: Patients were diagnosed as hypothermic (mean body temperature <36°C or 96.8°F) or not upon admission to the R.R. Incidence of hypothermia as a function of patient sex, transfusion during surgery or R.R., whether or not the O.R. had laminar flow, whether the patient was admitted to the R.R. with endotracheal tube in place, and A.S.A. classification was examined. Further, type of oxygen therapy, anesthetic technique, and surgical procedure were examined for related differences in incidence of hypothermia. The overall incidence of hypothermia was 55.6% (173 of 312 patients). Transfusion during surgery or R.R. increased the incidence to 78.4% (29 of 37) ($x^2(1) = 7.9$, $p<0.01$).Patients admitted from O.R.'s with laminar flow showed a higher incidence (84%, 21 of 25)($x^2(1)=7.74, p<0.01$). Patients admitted with the endotracheal tube in place showed an increased incidence of hypothermia (71.6%, 48 of 76) ($x^2(1) = 8.24$, $p<0.01$). There was a progressive increase in incidence of hypothermia as a function of ASA classification. Any form of oxygen therapy other than a simple face tent was predictive of hypothermia. With the face tent alone, the incidence was 50.5%. When more complex forms of therapy were required, 93.9% of the patients exhibited hypothermia ($x^2(1) = 20.6$, $p<0.01$). Type of anesthetic was not related to the incidence of hypothermia ($x^2(7) = 11.5$, $p>0.10$). Though the surgical procedure employed did show a relationship to the likelihood of hypothermia, the frequencies with which each procedure was used made specific procedure interpretation difficult. In general, longer, more invasive procedures had a greater likelihood of producing hypothermia.

Discussion: These findings further support the incidence of hypothermia in the R.R. and the indication for careful temperature monitoring during the perianesthetic period. Furthermore, specific therapies have been identified as increasing the risk of hypothermia. This information should lead the practitioner to thoughts about preventing or reducing the risk in these target groups.

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INCIDENCE OF HYPOTHERMIA AS A FUNCTION OF A.S.A. CLASSIFICATION

	A.S.A. Classification			
	I	II	III	IV & V
HYPOTHERMIC	42.8%	57.3%	60.3%	93.3%
NONHYPOTHERMIC	57.2%	42.7%	39.7%	6.7%

TITLE: A COMPARISON OF INTRATHECAL AND EPIDURAL MOPRHINE FOR TREATMENT OF POST-THORACOTOMY PAIN

AUTHORS: G. A. Fromme, M.D.; J. R. Gray, M.D.

AFFILIATION: Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905

Introduction. Post-thoracotomy pain is accompanied by many unwanted physiologic changes. Splinting and ineffective cough lead to decreases in vital capacity, tidal volume, FRC, FEF_{25-75} and FEV_1, all of which contribute to secretion retention, atelectasis, pneumonia, hypoxia and respiratory failure. These pulmonary function changes are greatest at 24-72 hrs and may persist for 10-14 days.[1] Since patients undergoing thoracotomy generally have abnormal pulmonary function prior to surgery, and are having variable amounts of functional lung tissue resected, they demand the optimal method of pain control. It has been shown that these changes are attenuated, but not eliminated by epidural morphine sulphate (EMS),[2] epidural local anesthetics,[2] intercostal nerve block[3] and transcutaneous nerve stimulation.[4] Intrathecal morphine sulphate (ITMS) has also been used for control of postoperative pain. This study was done to compare analgesic effectivenss of epidural morphine with intrathecally administered morphine.

Methods. We retrospectively reviewed the histories of 50 patients managed with intrathecal morphine following thoracotomy (Group I), and compared them with 129 post-thoracotomy patients who were treated with intermittent injections of morphine through an epidural catheter (Group II). Both groups received general anesthesia with an inhalation agent and intravenous narcotics. All patients were extubated in the recovery room where Group I patients were given intrathecal morphine sulfate in an average dose of 0.79 mg. Doses ranged from 0.5-1.2 mg. Group II patients received their initial epidural morphine injection while in the recovery room. The epidural dosage averaged 6.2 mg and ranged from 3.0-10 mg. Repeat injections in Group II were generally made with the same dosage unless side effects or inadequate analgesia suggested a change. All patients were nursed in postsurgical ICU where repeat epidural injections were available on a 24-hour basis, as were additional analgesics if either intrathecal or epidural morphine were ineffective. We tabulated the percentage of patients in whom analgesia was inadequate in both groups as well as duration of analgesia provided.

Results. Only 3 patients out of 50 (6%) in Group I requested additional analgesics prior to 16 hours after injection of intrathecal morphine sulfate. This did not differ significantly from the 7 out of 129 (5.4%) who requested additional analgesics during administration of epidural morphine (Chi square analysis). 8 of 50 patients (16%) receiving ITMS required no parenteral narcotics during their entire hospital stay. The mean duration of analgesia for ITMS was 20.83 ± 5.96 hours. The mean duration of analgesia in the EMS group was 50.58 ± 26.05 hours with a mean 4.29 injections per patient. The mean duration per injection was 11.8 hours. 1 out of 50 patients (2%) in Group I and 2 out of 129 patients (1.6%) in Group II required narcotic antagonists due to elevated $PaCO_2$ longer than 4 hrs after injection of ITMS or EMS. This difference was not statistically significant (Chi square analysis).

Discussion. This study demonstrates that both intrathecal and epidural morphine provide excellent relief of post-thoracotomy pain. ITMS has the advatages of technical simplicity, less risk of bleeding and infection since no indwelling material is used, and lack of need for in-house personnel available for reinjection. However, we feel that the epidural route may be more advantageous since catheter placement affords convenient access for reinjection which can significantly extend the duration of analgesia through the period of maximal depression of pulmonary function (see Figure).

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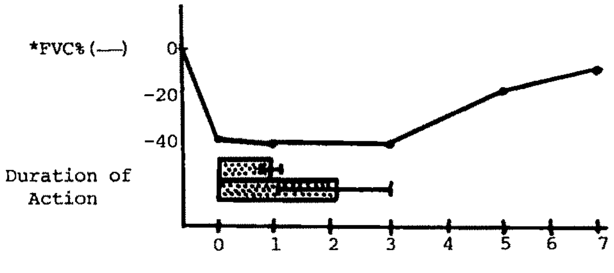

Percentage decrease in forced vital capacity (FVC)* and duration of action of ITMS and EMS plotted against postoperative day.

*Redrawn from Ali et al.

Title: ADRENERGIC FUNCTION DURING CARDIOPULMONARY BYPASS IN THE DOG

Authors: D Gaba, M.D., M Maze, M.B., S Metz, M.D., C Smith, M.Sc., V Henderson, M.D., C Miller, M.D.
Affiliation: Departments of Anesthesia and Cardiac Surgery, Stanford University School of Medicine;
Anesthesia Service and Cardiovascular Surgery Service, Palo Alto Veteran's Administration
Medical Center, Palo Alto, CA 94304

Introduction. Cardiopulmonary bypass (CPB) is associated with markedly abnormal cardiovascular physiology (1). The responsiveness of the vasculature to alpha-1 adrenergic stimulation might be diminished in the setting of CPB, since relatively large doses of phenylephrine (PE), an alpha-1 agonist, are often required to support blood pressure during normothermic CPB. We have investigated the response of the vasculature to PE infusion in dogs undergoing CPB.

Methods. Anesthesia was induced in six female mongrel dogs with IV etomidate (3 mg/kg) and dilaudid (1.5 mg/kg), and maintained with etomidate (6 mg/kg/hr) and dilaudid (0.4 mg/kg/hr). After tracheal intubation, controlled ventilation was initiated. Mean arterial pressure (MAP), central venous pressure (CVP), ECG, and end-tidal CO_2 were continuously recorded on a polygraph. The right atrium and aorta were cannulated through a right thoracotomy. A Pemco, Inc. Heart Pump with Harvey H-800 bubble oxygenator was primed with 1.2 - 1.5 liters of lactated Ringers and hetastarch. Normothermic extracorporeal perfusion was initiated with the flow increased to achieve a MAP of 60-80 torr. A flow of 150 cc/min/kg was not exceeded. Arterial blood gases were measured and sodium bicarbonate added to maintain a normal pH. After 10 minutes the pressor dose-response to PE was tested. The baseline MAP and CVP were noted along with pump flow rate. Repeated doses of PE (4,8,16,32,64 µg/kg) were infused into the output port of the pump oxygenator over one minute each, followed by a one minute wait. The maximum MAP and CVP seen during a dose infusion or in the following minute was recorded. The systematic vascular resistance (SVR) was computed at baseline and after each dose from the known pump flow, MAP and CVP. The difference between each post-infusion SVR value and that at baseline was defined as delta SVR for that PE dose. This PE infusion protocol was completed over a ten minute period, and was immediately repeated. Central cooling (nasopharyngeal temperature 30 +/- 1°C) was begun and maintained for 60 minutes, followed by rewarming to pre-cooling temperatures. Two PE infusion studies were performed immediately after rewarming was complete. The animal was then sacrificed by lethal injection and CPB terminated. Curves of the $\log_{10}$ phenylephrine dose versus delta SVR were constructed and the least squares quadratic fit was computed by polynomial regression. The PE dose required to cause a 500 resistance unit change (ED 500) and a 2000 resistance unit change (ED 2000) in SVR was derived for each curve. All values were compared to those at the beginning of CPB. Differences were tested for statistical significance ($p < 0.05$) using ANOVA with repeated measures followed by the paired t-test.

Results. A representative set of PE pressor dose-response curves for a single animal during CPB is shown in figure 1. There was a significant ($p < 0.05$) increase in both ED 500 and ED 2000 between the beginning and end of CPB as shown in figure 2.

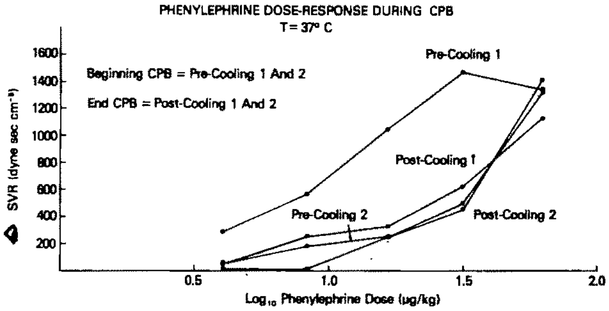

Figure 1. Representative semi-logarithmic dose response curves. Note shift to right of succesive curves. Elapsed time between pre-cooling curves is 15 minutes.

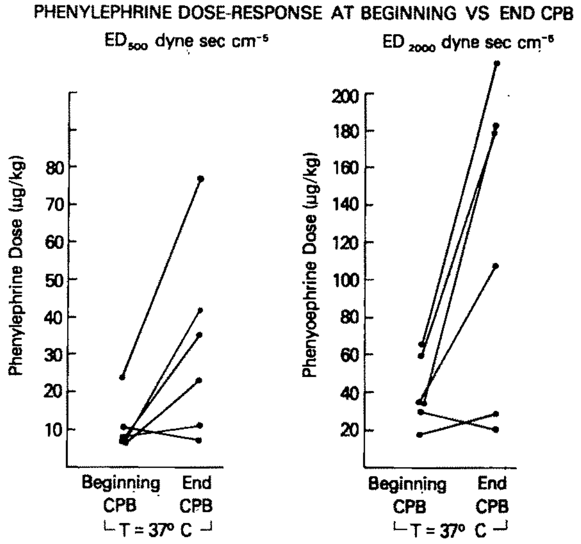

Figure 2. ED 500 and ED 2000 at beginning and end of CPB. A much higher PE dose is required at end CPB indicating development of alpha-1 hyporesponsiveness during CPB.

Discussion. Vascular responsiveness to alpha-1 adrenergic stimulation was significantly decreased during CPB. Alpha-1 hyporesponsiveness often developed very rapidly, within 25 minutes of initiating CPB. The trigger for the development of alpha-1 adrenergic hyporesponsiveness during CPB is unknown but might involve changes in viscosity, non-pulsatile flow, or high circulating catecholamine levels. The development of hyporesponsiveness to alpha-1 stimulation during CPB has important ramifications for the clinical treatment of patients during and after CPB.

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Title: ADRENERGIC OR CALCIUM CHANNEL BLOCKADE DOES NOT PREVENT POST-COUNTERSHOCK MYOCARDIAL DAMAGE IN HALOTHANE ANESTHETIZED DOGS

Authors: DM Gaba, M.D., S Metz, M.D., and M Maze, M.B., Ch.B.
Affiliation: Department of Anesthesia, Stanford University, Anesthesia Service, Palo Alto Veteran's Administration Medical Center, Palo Alto, CA 94304

Introduction. Necrotic myocardial lesions can be produced by transthoracic direct current electric countershock (CS) in animals as well as humans. Because the lesions are histologically similar to those seen after high doses of catecholamines (1), and are associated with calcium overload we investigated whether adrenergic or calcium channel blockade could attenuate or eliminate these lesions in adult dogs.

Methods. Twenty mongrel dogs were anesthetized with halothane 1.5% in oxygen by mask. The trachea was intubated without relaxants and ventilation controlled to achieve an end-tidal CO_2 of 4%. An intravenous catheter and a femoral arterial catheter were placed percutaneously. Lead II of the ECG, arterial pressure, end-tidal CO_2 and halothane concentration were continuously recorded. Mean arterial pressure (MAP) was stabilized to > 60 torr by infusion of normal saline or Ringer's lactate, and reduction of halothane to a minimum of 1.25%. An infusion of one of 4 drugs was given: Saline; prazosin (0.1 mg/kg), an alpha-1 antagonist; metoprolol (0.5 mg/kg), a beta-1 antagonist; or verapamil (0.5 mg/kg), a calcium channel antagonist. Five minutes after drug infusion two transthoracic countershocks of 295 delivered joules each were administered at one minute intervals with 8 cm paddles well coated with conducting cream. Following CS ventricular arrhythmias were treated with lidocaine (1.5 mg/kg) or atropine (0.2 mg) as required. The animals were then recovered from anesthesia. 24 hours later 10 - 12 mCi of technetium-99m pyrophosphate (Tc-PYP) was injected. One hour later the animal was sacrificed and the heart removed. Any visible lesions were excised and cut into multiple specimens. An adjacent border zone was sampled as were the rest of the free walls and septum. All samples were weighed and counted for Tc-PYP activity in a gamma counter using a window of 120 - 160 kev.

After calculation of Tc-PYP activity as cpm/gram all values were expressed as a sample to normal ratio (SNR) by dividing by the average activity of multiple normal samples from the posterior left ventricular free wall. An SNR greater than 3.0 was considered evidence of myocardial damage (2). The mass-weighted average SNR, and the total weight, of all samples with a SNR > 3.0 were computed as standard measures of myocardial damage in each animal (2). These were compared between groups by one-way ANOVA followed by Dunnet's test for comparison of multiple groups to control. Values are mean ± standard error. Statistical significance was considered at $p < 0.05$.

Results. Myocardial lesions were seen in 4 out of 5 control dogs and in all but two dogs receiving active pretreatment (1 metoprolol and 1 prazosin). Tc-PYP uptake data revealed the following:

TABLE 1. Effect of Drug Pretreatment on Parameters of Myocardial Damage Following Transthoracic Countershock

Drug Group	Weighted Average SNR	Wt. of Tissue with SNR > 3.0 (grams)
Control (N = 5)	14.1 ± 3.9	1.58 ± 0.58
Prazosin (N = 6)	13.9 ± 3.9	2.99 ± 0.63
Metoprolol (N = 5)	10.6 ± 3.1	1.71 ± 0.68
Verapamil (N = 4)	21.5 ± 12.5	1.56 ± 0.68

No drug group differed significantly from control or from other groups.

Discussion. The etiology of post-countershock myocardial damage is unknown. Our results suggest that adrenergic mechanisms and calcium channel activity are not critically involved in its pathogenesis. Direct disruption of myocardial and subcellular membranes by countershock may be the cause of these lesions, as is suggested by their appearance under electron microscopy (3). The similarity of the histology of this lesion to that seen after administration of high doses of catecholamines probably represents a common expression of myocardial injury rather than a similar initiating mechanism.

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TITLE: HEMODYNAMIC EFFECTS OF ESMOLOL DURING FENTANYL ANESTHESIA FOR CABG

AUTHORS: D Girard MD, DM Thys MD, JA Kaplan MD, BP Mindich MD, PC Beers PhD, SK Mikula RN.

AFFILIATION: Departments of Anesthesiology and Surgery, The Mount Sinai School of Medicine, One Gustave Levy Place, New York City, NY 10029.

INTRODUCTION Esmolol is a new intravenous beta-adrenergic blocker with a distribution half-life of 2 minutes and elimination half-life of 9 minutes. The aim of this study was to determine the safety and effect of various doses of esmolol on systemic hemodynamics during high-dose fentanyl anesthesia for coronary revascularization.

METHODS After institutional approval and written informed consent had been obtained, 20 patients scheduled for elective CABG were randomly assigned to an esmolol or placebo group. The study was conducted in a double blind fashion. In patients who were preoperatively on beta blockers or calcium blockers, the drugs were withheld for at least 2 half-lives prior to the beginning of the study-period. Premedication consisted of diazepam .1 mg/kg P.O. 90 minutes before surgery, morphine .1 mg/kg IM and scopolamine .4 mg IM 60 minutes before surgery. After insertion of monitoring lines (radial and pulmonary artery catheters), anesthesia was induced with fentanyl 75 mcg/kg, pancuronium .15 mg/kg, and 100% O_2. The study medication was infused in a stepwise manner to obtain an esmolol administration rate of 100, 200, and 300 mcg/kg/min. Each dosage level was maintained for 10 minutes and was preceded by a loading dose of 500 mcg/kg/min for 1.5 minutes. Hemodynamic measurements and blood samples were obtained before anesthesia, before drug infusion (baseline), at the end of each administration level, and at 5, 15, and 30 minutes after termination of the infusion. No surgical stimulation occurred during the infusion period. The drug was discontinued if any patient became hemodynamically unstable. Data were analyzed using Student's unpaired T-test for comparison between groups and paired T-tests for comparison within the groups. All values are expressed as mean ± SD.

RESULTS (See Figure) During infusion of esmolol, the pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), and systemic vascular resistance (SVR) were significantly higher than at the time of the baseline measurement. At the end of the 300 mcg/kg/min infusion, the CI was significantly decreased by 21%. However, similar changes in PCWP and CI were observed in the placebo group. As a result, the only significant difference between the esmolol and placebo group was a higher SVR in the esmolol group at the end of the 100 and 200 mcg/kg/min infusion. Three patients had to be eliminated from the study because their CI fell below a predetermined value of 2 L/min/m^2. Two of these patients were in the placebo group, the third one was at the end of the 200 mcg/kg/min esmolol infusion. No esmolol was present in the blood samples taken from the placebo patients. The steady state esmolol blood levels at each dosage were found to equal: 1.21±.267, 2.59±.607 and 4.19±1.13 mcg/ml corresponding to esmolol dosage levels of 100, 200, and 300 mcg/kg/min, respectively. At 5 minutes post-infusion the blood levels of esmolol were reduced to 8.4% of the peak levels seen at the 300 mcg/kg/min dose. By 30 minutes post-infusion, esmolol could be quantified in only 4 of 10 patients and those levels were less than 2% of the peak levels at 300 mcg/kg/min.

DISCUSSION Previous studies have shown that esmolol can safely and effectively be used to decrease ventricular rate in supraventricular tachycardia and to block the heart rate and blood pressure response to an isoproterenol challenge.[1,2] In our study, the extent of beta-blockade was not tested by surgical stimulation or a beta-agonist, but the blood levels of esmolol found were in the therapeutic range determined previously by other investigators.[2] The hemodynamic effects of esmolol during fentanyl anesthesia without indication for beta-blockade were minimal. Surprisingly the heart rate in the esmolol group and the placebo group were not different. Possible explanations include the very low sympathetic tone during fentanyl anesthesia and the relatively low heart rate present at the beginning of the infusion. Although myocardial depression was suggested by an increased PCWP and decreased CI, in all patients these changes were reversed within 15 minutes of drug discontinuation. Thus it appears that, under the circumstances of this study, the administration of esmolol is safe.

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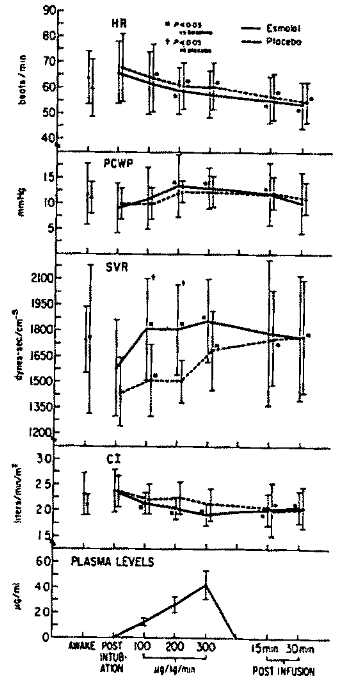

Title: BLOOD HISTAMINE LEVELS DURING TRIMETHAPHAN-INDUCED HYPOTENSION

Authors: D. Glauber, M.D., P.S. Colley, M.D., R. Haschke, Ph.D., A. Artru, M.D.

Affiliation: Department of Anesthesiology, University of Washington School of Medicine, Seattle, WA 98195

Introduction. It is commonly stated in textbooks (1,2) that trimethaphan camsylate (Arfonad^{R}) may cause the release of histamine. This statement is repeated in the package insert which recommends caution in its use in allergic individuals. It is also speculated that the released histamine augments the ganglionic blocking effect of trimethaphan to produce hypotension. However, there are no documented reports of histamine-related side-effects with this drug, and blood levels of histamine during trimethaphan-induced hypotension have never been reported. Reported evidence (3,4) for release of histamine comes from studies done before reliable and sensitive assays were available. We therefore studied histamine release in patients undergoing surgery in which trimethaphan was used to produce controlled hypotension. Blood histamine levels were determined using a recently developed sensitive radio-immune assay. (5)

Methods. This study was approved by the Human Subjects Committee. Twelve ASA-I patients (ages 14-43 years) with no history of allergy or antihistamine use gave informed consent for the study. All patients underwent maxillo-facial surgery requiring nasal intubation. Premedication was with oral diazepam only. Anesthesia induction was with thiopental 2-3 mg/kg sometimes in combination with fentanyl 2-3 µg/kg. On four occasions, succinylcholine was used to facilitate intubation. In all other cases intubation was accomplished by the nasal route blindly during spontaneous ventilation. Dexamethasone 8 mg was given intravenously after induction to minimize the edema of surgery. Where feasible (8 patients) the radial arterial line was placed while the patient was awake and a control sample of blood was taken with the patient breathing room air. In 4 patients, the radial line was placed after induction and intubation, and the initial and subsequent samples were taken during anesthesia maintenance with 1-2% isoflurane in nitrous oxide and oxygen (50:50). Trimethaphan 0.1% in 5% Dextrose was infused via an IMED^{R} pump. Arterial blood samples in heparinized syringes were taken, centrifuged within 30 minutes of sampling and immediately frozen. Sampling began just prior to commencement of trimethaphan infusion followed by three further samples at 5 minute intervals and a fifth sample when the hypotensive goal (MAP 50-60 mmHg) was reached. Cumulative trimethaphan dose was recorded. Statistical analysis was by paired t-test.

Results. No patient showed any clinical evidence of histamine release. There were no significant changes in blood histamine levels comparing the "room air" specimens to the control (post-anesthetic but pre-trimethaphan) specimens. Comparison of pre-trimethaphan histamine levels to those at the later sampling times showed no significant changes in mean levels at any time (Fig.) The hypotensive goal was reached at an average of 22 minutes (18-25 min.) after start of infusion. Average dose at this point was 26 mg (0.41 mg/kg body weight), and no correlation between drug dose and histamine levels could be found. Histamine levels at the end of the trimethaphan infusion (n=5) after an average total dose of 141 mg were not significantly different from control levels. An additional 10 patients were studied using the same protocol but without exact recording of trimethaphan dosage. Here too there were no significant changes in mean blood histamine levels.

Discussion. Normal blood histamine levels range from 300-1,000 pg/ml. Following bolus administration of histamine-releasing drugs. histamine blood levels reach maximum levels at 2-5 minutes and return to control values at 5-10 minutes.^{5,6,7} Hypotension results when blood histamine levels are >5,000 pg/ml^{8} or >200%^{9} above control values. The sampling frequency in this series was chosen to detect possible increases in histamine over a longer period when a drug is given by slow infusion rather than in a bolus. Occasional changes were detected, but they did not reach the levels associated with hypotension as a histamine effect. No correlation was observed between blood levels and blood pressure. This study finds no evidence that trimethaphan releases significant amounts of histamine and no evidence that histamine contributes to the hypotensive effect of the drug.

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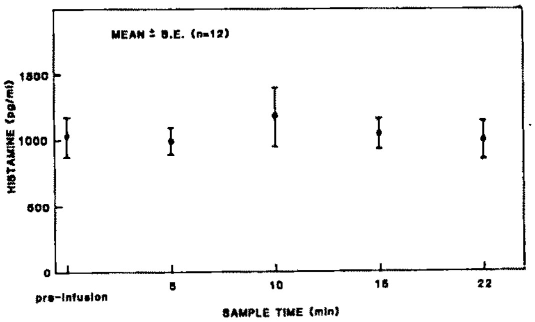


Title: ACUTE EFFECTS OF HALOTHANE ON DRUG DISTRIBUTION IN THE DOG

Authors: L Gordon, M.D., AJJ Wood, M.D., and M Wood, M.D.

Affiliation: Departments of Anesthesiology and Pharmacology, Vanderbilt University Medical School, Nashville, Tennessee 37232

Introduction. Inhalational anesthetic agents may influence drug disposition by two major mechanisms; firstly by acute alterations in drug distribution as may occur due to changes in protein binding or volume of distribution, and secondly, more slowly, by changes in drug elimination. It is well recognized that halothane causes hemodynamic changes and markedly alters peripheral blood flow. We postulated that halothane-induced changes in peripheral blood flow might cause acute alterations in drug distribution with consequent increase in plasma drug concentrations. This has important toxic implications for the intraoperative period. The purpose of the present study was to define the acute effect of the administration of halothane anesthesia on drug distribution in the dog using propranolol as a model compound.

Methods. Five dogs (21.7 ± 2.2 kg) were anesthetized with intravenous pentobarbital (30 mg/kg), tracheal intubation performed and ventilation with 100 percent oxygen was controlled to maintain arterial blood gases within the physiological range. Cannulae were placed in the femoral artery, femoral vein and a peripheral vein. Each dog received a loading dose of 6 mg propranolol administered over 10 minutes using a constant infusion pump into the peripheral vein. The infusion rate was then reduced to a maintenance rate of 0.058 mg/min for the duration of the study. After 90 minutes of propranolol administration, femoral arterial and venous blood samples were obtained simultaneously every 10 minutes over a 60 minute period. Halothane anesthesia was then administered to achieve an end tidal concentration of 2.0 MAC (1.74 percent) which was monitored using the Engstrom gas analyzer (EMMA). End tidal halothane concentrations were also determined by gas chromatography. Further femoral arterial and venous samples were then collected simultaneously every minute for 5 minutes following the start of halothane anesthesia, every 2 minutes for the next 10 minutes, and then at 30, 45, 60, and 120 minutes after the start of halothane anesthesia. Propranolol concentrations in arterial and venous plasma were measured by high performance liquid chromatography. The statistical significance of differences were determined by analysis of variance and students' t test for paired values with $p < 0.05$ being taken as the minimal level of significance.

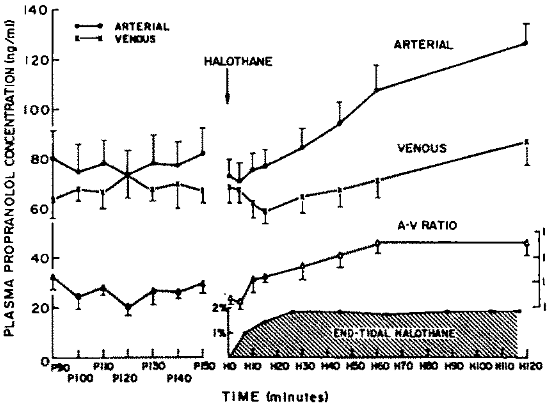
Results. A halothane concentration of 2.0 MAC was achieved 20.2 ± 2.3 minutes after starting halothane administration. The acute effect of the administration of halothane on arterial and venous plasma propranolol concentrations is shown in the figure and table. During the period preceeding halothane administration, propranolol levels were remarkably constant with the arterial levels being approximately 10% higher than the venous levels. However, following halothane administration the arterial levels rose rapidly with initially little change in venous concentrations so that the arterial to venous concentration ratio (A-V ratio) increased by 35% from 1.13 to 1.52 sixty minutes after starting halothane. Venous propranolol concentrations took longer to increase and were significantly increased only 120 minutes after starting halothane.

Discussion. Halothane has been shown to inhibit drug metabolism *in vivo*. This study has shown that halothane also affects drug distribution. The rapid rise in arterial propranolol concentration following halothane administration with no change in venous concentrations for the first hour resulted in an increase in the arterial to venous concentration ratio. This change implies that halothane causes a substantial and rapid change in drug distribution to tissues resulting in a 62% increase in arterial drug concentration. The mechanism responsible for this change is unclear at present but may involve changes in both drug binding and delivery to tissues. In the clinical setting, halothane's ability to inhibit drug metabolism and to alter drug distribution will be additive resulting in increased drug concentrations.

TABLE: EFFECT OF HALOTHANE ON PROPRANOLOL CONCENTRATIONS

	Time (mins)	Arterial Propranolol ng/ml±SEM	Venous Propranolol ng/ml±SEM	A-V ratio ±SEM
Pre halothane	90	80.2±11.07	64.2±7.5	1.25±0.09
	100	75.0±10.7	67.8±4.9	1.09±0.09
	110	78.2±9.7	66.6±6.1	1.16±0.05
	120	73.6±9.3	73.6±9.4	1.00±0.05
	130	77.8±11.5	67.6±4.7	1.13±0.10
	140	77.5±9.2	69.8±9.9	1.12±0.04
	150	82.0±9.9	67.6±5.2	1.20±0.08
Mean pre-halothane		77.47±9.8	68.23±6.3	1.13±0.06
Post-halothane	5	71.0±7.3	67.6±5.4	1.05±0.05
	10	75.4±6.5	62.2±5.9	1.23±0.10
	15	76.8±6.6	58.5±4.9	1.25±0.05
	30	84.2±8.0	64.4±6.3	1.32±0.10
	45	93.8±9.0*	67.0±6.6	1.42±0.10
	60	107.2±10.1*	71.2±7.3	1.52±0.08*
	120	126.2±7.5*	85.8±9.1*	1.50±0.10

*$p < 0.05$ compared to pre-halothane



Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University

Title: ATRACURIUM INFUSION IN CHILDREN ANESTHETIZED WITH HALOTHANE, ENFLURANE AND N_2O/O_2 NARCOTICS

Authors: NG Goudsouzian, M.D., and B Smith, RAT
Affiliation: Department of Anaesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA
and the Medical Department, Burroughs Wellcome Company, Research Triangle Park, NC

Atracurium has a relatively short duration of action compared to other nondepolarizing neuromuscular blocking agents and can be administered via continuous infusion to maintain a consistant degree of neuromuscular paralysis throughout surgical procedures. In this study we evaluated the neuromuscular effect of atracurium when given at a continuous infusion in children anesthetized with halothane, enflurane and N_2O/O_2 narcotic anesthesia.

METHODS

The protocol of this study was approved by the Human Studies Commission of our institution and parental written consent was obtained. Fifteen children, 1-10y old (mean±SE 4.3±0.8y), were studied. They were premedicated with rectal methohexital (25-30mg/kg) and divided at random into 3 groups of 5. The first group received N_2O/O_2 halothane (1% inspired) anesthesia, the second group received N_2O/O_2 enflurane (2% inspired) and the third group N_2O/O_2 morphine (0.1-0.25mg/kg) anesthesia. After induction of anesthesia, the ulnar nerve was supramaximally stimulated with repetitive single twitch stimuli at 0.1Hz with skin surface electrodes. The force of contraction of the adductor of the thumb was recorded by a polygraph through a Grass FT-03 force displacement transducer.

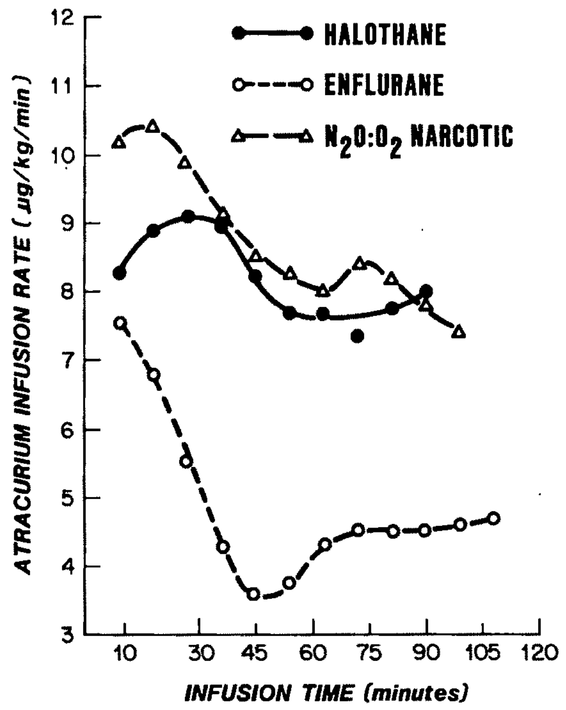
Following induction of anesthesia and stablization of the twitch recording for each patient, atracurium 0.4mg/kg was administered intravenously and the trachea intubated within the next three minutes. When the twitch started to recover atracurium infusion (200µg/ml) was begun. It was administered via a I-Med continuous infusion pump. The starting infusion rate for children anesthetized with halothane was 8µg/kg/min, with enflurane 6µg/kg/min and with N_2O/O_2 10µg/kg/min. The infusion rate was varied to maintain 90-99 depression of twitch height throughout the period of infusion. Near the end of the surgical procedure the infusion was discontinued and the patients were allowed to recover from the neuromuscular effect of atracurium. If needed, atropine 10µg/kg and neostigmine 30µg/kg were administered for antagonism.

RESULTS

The data of the neuromuscular effects of a bolus 0.4mg/kg dose of atracurium are summarized in Table 1.

Anesthetic Agent	Max Twitch Suppression % mean±SE	Inj - Max Twitch Suppression min±SE	Start of Recovery of Twitch min±SE
Halothane	99±0.5	3.5±0.35	18.3±1.6
Enflurane	98.8±0.6	4.5±1.1	20.3±3
$N_2O:O_2$ Narcotic	99.4±0.4	4.0±0.5	16.8±0.7

The mean atracurium infusion rate to maintain 90-99% suppression of the twitch is summarized in Fig 1.



The mean infusion rate to maintain 94.6±0.4% suppression of the twitch in children anesthetized with halothane and N_2O/O_2 narcotic anesthesia was 8.35±0.13 and 8.97±0.15µg/kg/min respectively. In children anesthetized with enflurane it was significantly less at 4.73±0.11µg/kg/min ($P<0.001$).

DISCUSSION

Children anesthetized with halothane and N_2O/O_2 narcotic require approximately 9µg/kg/min of atracurium to maintain satisfactory neuromuscular relaxation. Children anesthetized with enflurane (2%) require significantly less atracurium, about 5µg/kg/min. The enflurane potentiation of atracurium is time dependent and reaches its peak about one hour after the start of anesthesia.

The result in children anesthetized with N_2O/O_2 was not markedly different from that in adults studied under similar circumstances.(1)

Atracurium can be conveniently administered in children via continuous infusion to maintain satisfactory neuromuscular relaxation.

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TITLE : ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE IN FIVE MYASTHENIC PATIENTS

AUTHOR : SJ Greene, M.D., CA Shanks, M.D., AK Ronai, M.B., Ph.D., A Ramseur, M.D.

AFFILIATION: Department of Anesthesia, Northwestern University

INTRODUCTION: In patients with myasthenia gravis (MG) there is a greater than normal intensity of neuromuscular blockade following administration of nondepolarizing muscle relaxants. As atracurium has a shorter duration of action than the previously available nondepolarizing agents, it appeared to offer an advantage in the anesthetic care of patients with MG. When atracurium was administered to a preliminary patient with known MG, the drug requirements did not appear to be abnormal, leading us to study the neuromuscular blocking effects of this drug in five patients with MG.

METHODS: Five patients who gave their written informed consent to be studied were scheduled for elective surgery. Their clinical details appear in the table. Patients 3 and 4 underwent excision of a thymoma. Patients 1 to 4 continued to receive oral pyridostigmine therapy until the time of operation. Patient 5 had been receiving pyridostigmine, 120 mg every 6 hours, and alternate day steroid therapy until 10 days prior to operation. In all patients anesthesia was induced with thiopental, 300-500 mg, and maintained with a volatile inhalation agent, usually enflurane, 1.5 to 2.5%. Following induction of anesthesia, control values of the evoked twitch response were obtained, using the integrated compound electromyogram at the hand. Atracurium was then administered intravenously in 10 mg increments every 3 min until the response was less than 20% of the control value. Following tracheal intubation, ventilation was controlled to maintain end-tidal carbon dioxide at approximately 30 mm Hg.

RESULTS: The peak intensity of blockade, the interval from the last dose of atracurium, and the time to 25% of the control response are shown in the table. Further doses of atracurium after intubation were administered only to patient 5. None of the patients required antagonism of their neuromuscular blockade, based on a T4/T1 ratio in excess of 70% at the end of surgery. The endotracheal tube was removed from all patients within the first postoperative hour, at which time all patients were able to sustain head lift for greater than 10 sec and all had a negative inspiratory force greater than -20 cm water. The preoperative pyridostigmine therapy was recommenced in patients 1 to 4 within 24 h of surgery. Patients 1, 2, 3, and 5 had no evidence of postoperative pulmonary complications. At 48 h postoperatively, patient 4 required reintubation and mechanical ventilation for a two-day period.

DISCUSSION: Since beginning this study, two reports have appeared of single patients with MG receiving atracurium. In the first patient, atracurium was administered over 25 min in incremental doses totaling 8 mg, to provide "satisfactory" surgical conditions.[1] The other patient was intubated after divided doses of atracurium totaling 0.25 mg.kg^{-1} produced 90% paralysis.[2]

In normal patients a single dose of atracurium, 0.56 mg.kg^{-1} produced 10% paralysis, with recovery to 25% of control in an average of 45 min.[3] A dose of 0.33 mg.kg^{-1} produced greater than 98% block, with recovery to 25% of control in 28 min.[4] Patients 1 to 4, who received 0.42 ± 0.05 mg.kg^{-1}, recovered to 25% of control at an average of 39 min, suggesting a normal time-course of paralysis. However, the peak intensity of response was less than expected in these four patients. The fifth patient required a much lower dose, perhaps related to the early discontinuation of pyridostigmine therapy.

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Table: Clinical details.

Patient	1	2	3	4	5
Age, years	29	77	63	59	30
Sex	F	F	M	M	F
Weight, kg	75	70	83	81	95
Duration MG, years.	9	7	0.1	0.5	10
Current dose pyridostigmine, mg.	120 q2h	60 qid	90 q4h	60 q6h	Zero
Time since last dose, min.	90	240	135	420	-
Number of doses of atracurium, 10mg.	3	3	4	3	1
Peak effect, % control.	5%	6%	13%	3%	2%
Time to peak effect, min.	6	8	7	2	6
Time to 25% of control, min.	33	40	30	62	30

Title: THE EFFECT OF NIFEDIPINE ON ASPIRATION IN DOGS

Authors: J.K. Griffeth, M.D., D.L. Packer, M.D., and T.J. Gallagher, M.D.

Affiliations: Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida 32610

Introduction. Aspiration of acid gastric contents increases ventilation-perfusion (V/Q) mismatch, which decreases blood gas exchange and increases venous admixture (Qsp/Qt). Increases in pulmonary artery pressure may contribute to hypoxemia and decreased cardiac output. This study was undertaken to determine, in a canine aspiration model, the effect of nifedipine on pulmonary artery pressures and subsequently on gas exchange and cardiac performance.

Materials and Methods. Ten healthy mongrel dogs (17-28 kg) were anesthetized with a continuous infusion of pentobarbital, intubated with an 8-mm endotracheal tube, and placed supine. Mechanical positive pressure ventilation was applied at a tidal volume of 12-15 ml/kg and a rate of 10 breaths/min (F_IO_2 = 0.24). Lactated Ringer's solution was infused at 2 ml/kg/h to keep pulmonary capillary wedge pressure within 2-4 mmHg of the baseline pressure. Monitoring included a 7-Fr balloon tipped thermal dilution pulmonary artery catheter inserted via the left internal jugular vein and a thermister tipped catheter (American Edwards Laboratory) inserted in the left carotid artery for calculation of extravascular lung water (EVLW) by the thermal-dye technique. Mean arterial (MAP), pulmonary artery (PAP), and pulmonary capillary wedge (PCWP) pressures, extravascular lung water (EVLW), and cardiac output were measured; arterial and mixed venous blood was sampled; and arteriovenous oxygen content difference ($C[a-v]O_2$), Qsp/Qt, pulmonary (PVR) and systemic (SVR) vascular resistances, and oxygen delivery (DO_2) were calculated by standard formulae. After baseline measurements, a solution of 15% ethyl alcohol, 15% polyethylene glycol 400, and 60% distilled water by weight with (n = 5) or without (n = 5) 250 mcg/kg of nifedipine was infused through the right atrium over 2-3 min. Measurements were repeated 10 min after the infusion. With animals in the head-up, left lateral decubitus position, 2 ml/kg of hydrochloric acid (pH = 1.8) was instilled into the endotracheal tube, which was repeated for the right lateral decubitus position (total aspirate: 4 ml/kg). Data were recorded 10, 45, 90, and 180 min after aspiration. Results were statistically evaluated by paired *t* test and regression analysis.

Results (Table). Before aspiration, nifedipine significantly decreased MAP and SVR ($P < 0.05$). After aspiration, SVR, PVR, and $C(a-v)O_2$ were significantly less and cardiac index (CI) significantly greater in dogs infused with nifedipine than in those infused without it ($P < 0.05$). In the nifedipine group, DO_2 and CI remained significantly greater beginning 45 min after aspiration than either before infusion or without nifedipine after aspiration. Pulmonary artery pressures were significantly increased only at 45 and 90 min after aspiration only in the nifedipine group.

Discussion. Nifedipine infusion before acid aspiration in this model had no direct affect on PAP, gas exchange, or EVLW; but the peripheral vasodilating effects of the drug appeared to significantly enhance CI such that DO_2 is significantly higher than control values after 45 min. Thus nifedipine may improve DO_2 in the early postaspiration interval. The increase in CI with nifedipine may have been responsible for the increase in PAP at 45 and 90 min.

Table. Comparison of Hemodynamic and Cardiovascular Effects of Aspiration in Dogs Pretreated With Nifedipine (N) or Vehicle Alone (V)

		Control	After Infusion	After Aspiration (min)			
				10	45	90	180
PaO_2 (mmHg)	N	106 ± 10	104 ± 11	47 ± 7*	65 ± 8*†	67 ± 6*†	68 ± 4*
	V	109 ± 31	83 ± 6	46 ± 8*	54 ± 4*	54 ± 6*	58 ± 11*
Qsp/Qt (%)	N	5 ± 5	8 ± 6	68 ± 5*	49 ± 11*	49 ± 9*	43 ± 17*
	V	7 ± 12	16 ± 6	56 ± 13*	47 ± 9*	51 ± 11*	37 ± 15*
EVLW (ml/kg)	N	10 ± 3	8 ± 2	10 ± 2†	10 ± 4	11 ± 2	13 ± 2†
	V	11 ± 2	11 ± 1	19 ± 8	18 ± 6	19 ± 8	23 ± 9*
CI	N	5.1 ± 1	7.3 ± 2*	6.2 ± 1*	7.3 ± 1*†	6.3 ± 1*†	6.2 ± 1*†
	V	4.9 ± 0.7	5.1 ± 0.2	4.5 ± 1	4.2 ± 1	4.2 ± 1	4.0 ± 1
DO_2 (ml O_2/min)	N	650 ± 300	940 ± 490*†	590 ± 170	910 ± 220*†	820 ± 250*†	780 ± 220*†
	V	550 ± 180	510 ± 40	350 ± 190*	360 ± 130	370 ± 130	390 ± 130
$C(a-v)O_2$ (ml/100 ml)	N	2.4 ± 0.4	2.5 ± 0.4	1.9 ± 0.3*†	1.8 ± 0.6†	1.8 ± 0.3*†	1.8 ± 0.4*†
	V	2.9 ± 0.3	2.5 ± 0.1	3.2 ± 0.8	32 ± 0.8	2.7 ± 0.5	4.1 ± 1.7
MAP (mmHg)	N	118 ± 12	52 ± 17*†	67 ± 7*	79 ± 18*	79 ± 11*	92 ± 7†
	V	111 ± 20	100 ± 10	84 ± 16*	81 ± 20	93 ± 14	117 ± 20
PAP (mmHg)	N	16 ± 8	19 ± 9	16 ± 5	20 ± 7*	19 ± 8*	19 ± 7
	V	12 ± 3	17 ± 1	16 ± 3	14 ± 4	18 ± 9	15 ± 6
PCWP (mmHg)	N	6 ± 4	8 ± 3	6 ± 3	8 ± 5	7 ± 3	6 ± 3
	V	2 ± 1	5 ± 0.7	3 ± 1	2 ± 1	4 ± 4	2 ± 2
SVR (dyne/sec/cm^{-5})	N	2098 ± 463	592 ± 163*†	973 ± 375*†	915 ± 222*†	1104 ± 26*†	1331 ± 386*†
	V	2320 ± 199	1972 ± 198*	2065 ± 843	1988 ± 695	2703 ± 1071	3575 ± 706*
PVR (dyne/sec/cm^{-5})	N	184 ± 48	130 ± 59	147 ± 36†	149 ± 20†	171 ± 35	184 ± 32†
	V	237 ± 54	249 ± 46	288 ± 15	298 ± 81	419 ± 277	404 ± 187

Values are means ± SD. Abbreviations are defined in the text of the abstract.

Continuation of Table.

*$P < 0.05$ compared with control.
†$P < 0.05$ compared with V at the same time.

Title: CARDIOVASCULAR EFFECTS OF DILTIAZEM INFUSION DURING FENTANYL ANESTHESIA

Authors: RM Griffin, M.D., I Dimich, M.D., V Pratilas, M.D., R Jurado, M.D., JA Kaplan, M.D.

Affiliation: Department of Anesthesia, Mount Sinai School of Medicine, One Gustave L. Levy Place,
New York, New York 10029

Introduction. Diltiazem is a calcium channel blocker used to treat variant and classic stable angina. In comparison to verapamil and nifedipine, diltiazem produces relatively less systemic vasodilatation and myocardial depression and greater depression of sinus node automaticity.[1] Since diltiazem is available in a water soluble non-light sensitive form, its hemodynamic properties may be used to induce hypotension and treat hypertension during anesthesia.[2] Previously, we have determined the hemodynamic effects of verapamil and nifedipine infusion during fentanyl anesthesia. The present study, therefore, allowed comparison with those observations whilst investigating the hemodynamic effects and, thus, potential use of diltiazem during fentanyl anesthesia.

Methods. Six dogs (19.0-24.0kg) were anesthetized with sodium thiopental (20mg/kg), intubated and ventilated to normocapnia with a mixture of 50% N_2O/O_2. Fentanyl (100mcg/kg) and pancuronium (0.1 mg/kg were given followed by continuous infusion of fentanyl at 1.0 mcg/kg/min. Heart rate (ECG lead II), right atrial pressure (RAP), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) and left ventricular dp/dt(LVdp/dt), via a Millar catheter, were continuously monitored. Passage of a 7FR pulmonary artery catheter via the femoral vein, provided pulmonary artery pressures, (PAPS,PAPD,MPAP) pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) determination (duplicate measurements). Systemic vascular resistance index (SVRI), cardiac index (CI) and left ventricular stroke work index (LVSWI) were calculated. PR interval (PR) was calculated from the ECG (50mm/sec). Control measurements were taken after 30 minutes of stable hemodynamic parameters, following instrumentation. Diltiazem HCL was dissolved in saline (2mg/ml) and 300 mcg/kg given as a bolus[2] followed by continuous infusion at 30 mcg/kg/min (D_1), 60 mcg/kg/min (D_2) and 90 mcg/kg/min (D_3). Each infusion period lasted 30 minutes. Hemodynamic measurements were taken 2 minutes after the bolus and subsequently at 5, 15 and 30 minutes for each infusion. Calcium chloride (Ca), 20 mg/kg was given after D_3, followed after a further 5 minutes by isoprenaline infusion. The results were expressed as mean $\pm$ S.E.M. and evaluated by analysis of variance. $P < 0.05$ was considered significant.

Results. Mean hemodynamic variables are shown in the Table. Diltiazem produced significant reductions in SVRI and MAP. Although SBP was relatively unaffected, DBP was significantly ($P < 0.05$) reduced, LV dp/dt was only slightly decreased and CI significantly increased during each infusion. Other hemodynamic variables (RAP, MPAP, PCWP, LVSWI) were not significantly affected throughout the study. During D_1 and D_2 HR increased but fell below the control value ($P < 0.05$) during D_3. PR interval was consistently prolonged, significantly during D_2 and D_3. Five dogs developed 1° block, three during D_1. Four of these five dogs developed established 2° block (Type I and Type II), one during D_1, two during D_2 and one during D_3. In addition two dogs had episodes of junctional rhythm. Ca had no effect on PR and actually decreased the HR. Although SBP was significantly ($P < 0.05$) improved, MAP was unaffected and SVRI was further decreased. Isoprenaline caused a significant ($P < 0.05$) increase in HR.

Discussion. Diltiazem produced significant hypotension as a result of profound systemic vasodilatation. Myocardial contractility (dp/dt) was only minimally affected and cardiac output was augmented due to the reduction in afterload. When diltiazem was infused in swine during halothane anesthesia, SVR was unaffected and BP was reduced by depression of myocardial contractility.[3] Therefore, the mechanism of diltiazem-induced hypotension during fentanyl anesthesia is different and may be more acceptable if diltiazem is used to lower BP intraoperatively. However, although the chronotropic effects of diltiazem appear to be dose related, the effects on A-V conduction are unpredictable and may limit the use of the drug during anesthesia. Furthermore, Ca will not reverse the negative chronotropic and dromotropic effects or the peripheral vasodilatation induced by diltiazem. Isoprenaline may be used to treat severe bradycardia should this occur.

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TABLE

	CONTROL	D_1	D_2	D_3
HR (bpm)	109 ± 6.1$^+$	116 ± 11.7	111 ± 10.4	90 ± 13.0*
PR (mm)	0.12 ± 0.0	0.19 ± 0.02	0.21 ± 0.02*	0.22 ± 0.02*
MAP(mmHg)	105 ± 7.3	91 ± 4.9*	80 ± 3.6*	74 ± 2.5*
SVRI (dyn.sec/cm^5/m^2)	3249 ± 257	1830 ± 207*	1399 ± 208*	1138 ± 148*
CI (L/Min/m^2)	2.40 ± 0.20	4.05 ± 0.88*	4.67 ± 0.95*	4.93 ± 0.89*
dp/dt (mmHg)/sec)	1866 ± 217	1800 ± 282	1750 ± 268	1783 ± 175
PCWP (mmHg)	11.5 ± 0.70	12.8 ± 1.13	14.3 ± 0.80	15.1 ± 1.10

+(x±S.E.M) *$P < 0.05$ compared to control

Title: DOSE-RESPONSE CURVES FOR MIDAZOLAM INDUCTION IN PREMEDICATED ASA PS III AND IV PATIENTS

Authors: JB Gross, M.D., MW Edwards, M.D., CB Caldwell, M.D.

Affiliation: Departments of Anesthesia, University of Pennsylvania and Philadelphia Veterans Administration
Medical Center, Philadelphia, PA 19104

Introduction: The wide range of published induction doses for midazolam, 0.15 to 0.36 mg/kg (1,2), reflects the absence of quantitative dose-response data in the literature. In this study, we determined dose-response curves for abolition of the response to verbal commands, eyelash stimulation, and musculocutaneous pain in premedicated ASA PS III and IV patients. For comparison, we performed similar determinations with ketamine, another agent which is used to induce anesthesia in unstable patients.

Methods: Fifty-seven male patients, ASA PS III and IV, consented to participate in this study which was approved by our Institutional Review Boards. We excluded patients who used benzodiazepines or ethanol within five days of surgery, or who had coronary artery disease, hypertension or other contraindications to ketamine or midazolam. Patients took nothing by mouth for at least 8 hours before induction of anesthesia. We gave morphine sulfate 0.1 mg/kg and glycopyrrolate 4 mcg/kg i.m. 60±15 min before induction of anesthesia. After recording baseline blood pressure (oscillotonometer) and heart rate (ECG), we administered a pre-determined i.v. dose of midazolam (0.15 to 0.35 mg/kg) or ketamine (1.0 to 2.5 mg/kg) in a double-blind manner. At ten-second intervals, one investigator (J.B.G.) determined patients' responses to the command "open your eyes," to brushing of the eyelash (lash reflex), and to squeezing of the trapezius muscle. We administered up to three additional doses of midazolam (0.05 mg/kg) or ketamine (0.5 mg/kg) at two-minute intervals until all responses were abolished. Immediately after induction of anesthesia, before administration of any other drugs, we recorded post-induction heart rate and blood pressure values. Subjects who remained responsive after three incremental doses of midazolam or ketamine received thiopental 1.5 mg/kg to complete induction. We determined the fraction of patients in whom each response was abolished after a given cumulative dose of midazolam (0.15 through 0.45 mg/kg) or ketamine (1.0 through 2.5 mg/kg), and used weighted least-squares analysis of log-dose vs. probit curves for each response (3) to determine ED50 and ED95 values (with 95% confidence limits) for abolition of each response by each drug. Two-way analysis of variance determined the significance of heart rate, systolic and diastolic blood pressure changes accompanying induction of anesthesia with each agent (patients requiring supplemental thiopental were excuded from this part of the analysis). $P < 0.05$ indicated statistical significance.

Results: For midazolam, ED50's for abolition of response to verbal commands, eyelash reflex, and trapezius squeeze were 0.19, 0.24, and 0.36 mg/kg, respectively; corresponding ED95's were 0.35, 0.43, and 1.04 mg/kg (figure 1). For ketamine, ED50's for verbal commands, eyelash reflex, and trapezius squeeze were 0.9, 1.3, and 1.3 mg/kg; corresponding ED95's were 1.6, 2.3, and 4.3 mg/kg (figure 2). Midazolam induction (N=23) decreased systolic blood pressure from 138 to 128 mmHg ($P<0.005$); diastolic blood pressure remained unchanged at 71 mmHg, and heart rate increased insignificantly from 85 to 88 BPM. Ketamine induction (N=26) significantly increased systolic blood pressure (141 to 164 mmHg, $P<0.005$), diastolic blood pressure (71 to 88 mmHg, $P<0.005$), and heart rate (84 to 102 BPM, $P<0.005$).

Discussion: The ED50 values for abolition of responses by midazolam (0.19 to 0.36 mg/kg) are similar to the induction doses reported previously (1,2). By definition, however, ED50 abolishes a given response in only half of the population; ED95 (0.35-1.04 mg/kg for midazolam) more realistically estimates a reliable induction dose. Our ED95's of 1.6 to 4.3 mg/kg for ketamine are similar to previously reported induction doses for ASA III and IV patients (4), confirming the validity of our analysis. The 10 mmHg decrease in systolic blood pressure with midazolam induction is statistically but not clinically significant. In contrst, the 23 and 17 mmHg increases in systolic and diastolic blood pressures along with the 18 BPM increase in heart rate following ketamine induction could significantly increase myocardial oxygen demand in patients with coronary artery disease. We conclude that the induction dose of midazolam in premedicated ASA III and IV patients is between 0.35 and 1.04 mg/kg (depending on the response assessed), and that midazolam induction provides excellent hemodynamic stability in these patients.

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Figure 1:
Midazolam
Dose-Response
Curves

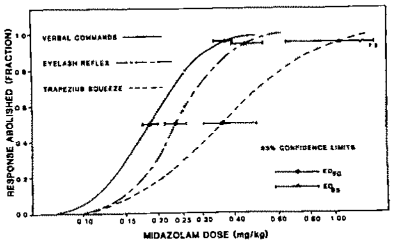
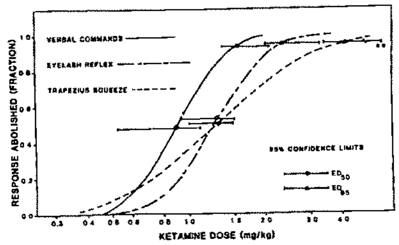


Figure 2:
Ketamine
Dose-Response
Curves



TITLE: COMPARATIVE MONITORING OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKADE IN HUMANS

AUTHORS: J HAM, M.D. AND JH REDPATH, M.D.

AFFILIATION: DEPARTMENTS OF ANESTHESIA: PALO ALTO MEDICAL FOUNDATION: SURGECENTER OF PALO ALTO: AND STANFORD UNIVERSITY, STANFORD, CALIFORNIA 94305

Introduction. During d-tubocurare neuromuscular blockade, monitoring with train of four (TOF) stimulation has demonstrated loss of the fourth (T4), third (T3), and second (T2) responses with 75, 80, and 90% disappearance of control responses respectively.[1] The purposes of this study are: (1) to evaluate TOF monitoring under clinical conditions for all currently available non-depolarizing muscle relaxants and (2) to compare responses of a small, hand-held, commercially available nerve stimulator to the standard laboratory equipment.

Methods. 25 healthy patients undergoing elective surgical procedures were randomly assigned into 5 study groups to receive d-tubocurare (dTc), pancuronium (P), dimethyltubocurare (M), gallamine (G), or atracurium (A). The study was approved by the institutional committee on human experimentation. Anesthesia was induced in unpremedicated patients with thiopental, 4-6 mg/kg, and continued by inhalation of halothane in nitrous oxide and oxygen (40%). Ventilation was maintained at a constant level. After induction, the inspired concentration of halothane was maintained at 1.5%. Force of thumb adduction in response to supramaximal ulnar nerve stimulation was monitored in both hands; one side utilized a Grass S88 stimulator (Gr) in conjunction with a Grass FT-10 force transducer and recorder; the other side utilized the hand-held "MiniStim" model MS-1 (MS) while manually feeling thumb adduction. Under stable conditions, 1 of the 5 muscle relaxants was administered in divided doses to produce gradual paralysis.[2] Neuromuscular blockade was continuously monitored at 0.15 Hz with Gr and intermittently TOF was applied after 10 seconds of silence with both units. Once 90-95% paralysis was achieved, spontaneous recovery was observed. Per cent paralysis was defined as the ratio of diminution of single twitch responses at 0.15 Hz to control. The response to TOF stimulation was considered absent when it was still visible but diminished 98-99% on the recorder. The data was analyzed by Analysis of Variance and the Newman-Keuls Test.

Results. The relationship of paralysis to loss of individual TOF responses during onset was similar for dTc, P, and M and agreed with a previous study except that T4 and T3 disappeared simultaneously in 28% of patients. With A, there was greater, and with G, less paralysis associated with loss of TOF responses. During recovery, there was less paralysis (6±4%) associated with return of TOF response for all drugs except M (-1±2%) where TOF responses returned during greater paralysis ($p<.05$). Responses to MS were somewhat subjective. Often, the TOF responses were not absent, so much as greatly reduced. In 80% of cases TOF responses with MS were less than Gr during onset and, in 64% of cases, greater than Gr during recovery. The difference usually consisted of 1-2 responses.

Table 1 Onset Paralysis vs TOF

	% paralysis with loss of		
	T4	T3	T2
A	86±4*	88±3**	93±2^t
P	82±4	83±4	91±2
dTc	79±4	84±2	90±1
M	76±4	78±2	88±1
G	72±5	80±4	87±2

Mean ±SD *$A \neq P = dTc = M \neq G$ ($p<.05$)
**$A \neq$ others ($p<.05$), t $A \neq$ others, $G \neq P = dTc$ ($p<.05$)

Table 2 Recovery Paralysis vs TOF

	% paralysis with return of		
	T4	T3	T2
A	76±5	81±2	88±4
P	76±8	79±7	86±5
dTc	74±8	76±11	86±4
M	77±5	81±2	87±1
G	67±5	81±2	81±3

Table 3 TOF MiniStim vs Grass

	Onset			Recovery		
	(+)	(0)	(-)	(+)	(0)	(-)
A	1	0	4	3	1	1
P	1	0	4	4	1	0
dTc	0	1	4	2	1	2
M	0	1	4	2	3	0
G	0	1	4	5	0	0

(+)=greater (0)=same (-)=less

Discussion. TOF monitoring must be individualized to the non-depolarizing muscle relaxant used. Quantitatively, loss of responses with A occur at greater paralysis during onset than other relaxants. During recovery, return of TOF responses occur with less paralysis for all drugs except M. A comparison of one hand-held nerve stimulator shows a rough correlation with standard laboratory techniques except for a tendency to underestimate paralysis during onset and overestimate paralysis during recovery.

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TITLE: RESPIRATORY EFFECTS OF ATRACURIUM IN HUMANS

AUTHORS: J. HAM, M.D. AND J.H. REDPATH, M.D.
AFFILIATION: DEPARTMENT OF ANESTHESIA, PALO ALTO MEDICAL FOUNDATION; SURGECENTER OF PALO ALTO, AND STANFORD UNIVERSITY, STANFORD, CALIFORNIA 94305

Introduction. Recently it was demonstrated that adequate spontaneous ventilation occurred shortly after tetanic and twitch responses first returned following paralysis produced by 0.3 mg/kg of atracurium.[1] In the older literature, the other non-depolarizing muscle relaxants have been associated with adequate tidal volume after recovery to 25% of control twitch response.[2] The purpose of this study is to evaluate the onset of and recovery from inadequate spontaneous ventilation (SV) during neuromuscular blockade from atracurium compared to the other non-depolarizing muscle relaxants available for clinical use in the United States.

Methods. 25 healthy patients undergoing elective surgical procedures were randomly assigned into 5 study groups to receive either atracurium (A), d-tubocurare (dTc), dimethyltubocurare (M), pancuronium (P), or gallamine (G). The study protocol was approved by the institutional committee on human experimentation. Anesthesia was induced in unpremedicated patients with thiopental, 4-6 mg/kg, and continued by inhalation of halothane in a nitrous oxide and oxygen (40%) during SV via a well fitted mask. After induction, the inspired concentration of halothane was maintained at 1.5%. Force of thumb adduction in response to supramaximal ulnar nerve stimulation was monitored utilizing a Grass S88 stimulator at 0.15 Hz in conjunction with a Grass FT-10 force transducer with recorder. Periodically stimulation was interrupted for 10 seconds and then a train of four (TOF) stimuli at 2 hz was delivered before resuming single stimulations at 0.15 Hz. The muscle relaxants were administered in divided doses to produce gradual paralysis.[3] Respiration was monitored by auscultation with a stethoscope and observation of the excursion of a 2 liter anesthesia bag attached to a circle breathing circuit. When tidal volume was judged inadequate by the investigator, controlled ventilation was initiated. Periodically during recovery from paralysis, the adequacy of SV was assessed. Eventually ventilation was allowed to continue unassisted when the previously adequate level returned. Per cent paralysis was defined as the ratio of the diminution of single responses at 0.15 Hz to control. The response to TOF stimulation was considered absent when it was diminished 98-99% on the recorder. The data was analyzed by Analysis of Variance and the Newman-Keuls Test.

Results. Spontaneous ventilation became inadequate with less paralysis of the thumb adductors with A compared to the other non-depolarizing relaxants. Two patients receiving A stopped SV with as little as 23% and 29% thumb paralysis. Similarly, fade of T4 during TOF was less depressed with loss of SV from atracurium compared to the other drugs. During spontaneous recovery from paralysis, adequate SV occurred at a similar extent of thumb adductor paralysis in all groups averaging 80±5% for all patients. The variability of response was such that one patient had adequate ventilation with 89% thumb paralysis and another with only 69%. TOF responses during spontaneous recovery were variable when adequate SV returned ranging from T1 to T4 but 52% of all patients had a T2 response. The difference between thumb paralysis with loss and recovery of SV (ΔR) was greater for atracurium than the other drugs.

Table 1

	Onset CV		Recovery SV	Δ R
A	38±11*	.53±.16*	81±9	43±13*
G	57±7	.19±.07	80±5	23±7
M	64±5	.17±.06	79±4	15±3
P	66±8	.34±.10	79±5	13±7
dTc	70±8	.28±.09	83±4	10±4

mean±SD *A≠others ($p < .01$)

Discussion. After administration of atracurium, SV becomes inadequate sooner and with less paralysis of the thumb adductors compared to dTc, M, G, and P. The mechanism is unknown but may include CNS or diaphragm receptor sites. Clinical implications include the following. (1) Disappearance of SV may be an inadequate sign for good intubating conditions with atracurium. (2) Atracurium may be desirable in a technique employing a non-depolarizing muscle relaxant where rapid control of ventilation is desirable.

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TITLE: α_1 BLOCKADE BY DROPERIDOL RAISES THE THRESHOLD FOR HALOTHANE-EPINEPHRINE ARRHYTHMIAS IN DOGS

AUTHORS: E Hayward, B.S., S Metz, M.D., D Gaba, M.D., CM Smith, M.Sc., C Spiss, M.D., and M Maze, M.B.

AFFILIATION: Departments of Anesthesia, Stanford University and the Veteran's Administration Hospital,
Palo Alto, CA 94304

INTRODUCTION: Prazosin, a selective α_1 adrenergic antagonist, raises the dose of epinephrine required to induce arrhythmias in dogs anesthetized with halothane (1). Because only a supra-maximal α_1 adrenoceptor blocking dose of prazosin was used, we could not exclude the possibility that a non-specific dose-independent mechanism, rather than α_1 blockade, was responsible for its anti-arrhythmic effect. Droperidol is a parenteral α_1 blocking agent which, like prazosin, possesses anti-arrhythmic properties (2). We hypothesize that droperidol's anti-arrhythmic effect is due to its α_1 blocking properties, and that as dose-dependent α_1 blockade increases, so will its anti-arrhythmic activity.

METHODS: Anesthesia was induced and maintained in seven unpremedicated dogs with halothane 1.5% in oxygen. Dogs were intubated without muscle relaxants and ventilated to achieve normocarbia. Arterial pressure was continuously monitored by a femoral catheter. Five percent dextrose in 0.2% NaCl with 89 mEq/L of $NaHCO_3$ was infused through a foreleg vein at 4 ml/kg/hr. After achieving a steady-state for 45 min phenylephrine, a selective α_1 agonist, was infused at various concentrations and the arterial pressure recorded. The dose of phenylephrine causing a 25 mm Hg increase in mean arterial pressure (ED_{25}) was derived by polynomial regression analysis of the semi-logarithmic dose-response curve and was used as a measure of α_1 adrenergic responsiveness. Using known pharmacokinetic parameters, droperidol infusion regimens were calculated to produce steady-state plasma concentrations of 50, 150, and 500 ng/ml. The ED_{25} was then redetermined at each of these plasma concentrations of droperidol and was used as a measure of α_1 adrenergic blockade.

In a second set of experiments, dogs (n=7) were anesthetized and monitored as described above and the arrhythmogenic dose of epinephrine (ADE) determined. The ADE was defined as that dose of epinephrine (μg/kg/min) required to produce 4 or more ventricular ectopic beats within 15 seconds. Epinephrine doses were logarithmically increased after ten minute recovery periods until an arrhythmia was produced and the ADE thereby established. The ADE was then redetermined at each of the steady-state plasma concentrations of droperidol and was used to quantitate the anti-arrhythmic action of this drug.

The changes in both the ED_{25} and ADE at each of the droperidol concentrations (0, 50, 150, and 500 ng/ml) were compared by analysis of variance for repeated measures followed by pairwise comparisons of successive values using the paired t-test with a Bonferroni correction for multiple comparisons.

RESULTS: The ED_{25} significantly increased with the rise in droperidol concentration (figure 1). There was a similar significant rise in the ADE over the same range of droperidol concentrations (figure 2). At each successive concentration of droperidol, the ED_{25} and the ADE was significantly greater than the previous value ($p < 0.05$).

The correlation between the ED_{25} (α_1 blockade) and ADE (anti-arrhythmic effect) (figure 3) was highly significant ($p < 0.001$) demonstrating proportional changes in these parameters as the droperidol concentration increased.

DISCUSSION: These data demonstrate that the anti-arrhythmic effect of droperidol may be a direct result of its α_1 adrenoceptor antagonist action. Droperidol may therefore be an appropriate agent in the treatment of epinephrine-induced arrhythmias under halothane anesanesthesia. Furthermore, parenteral α_1 adrenergic antagonists may become useful agents in the treatment of catecholamine-induced arrhythmias in other clinical settings.

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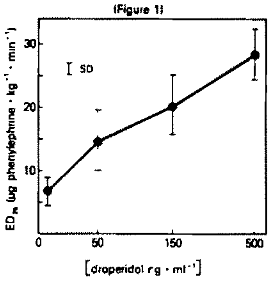
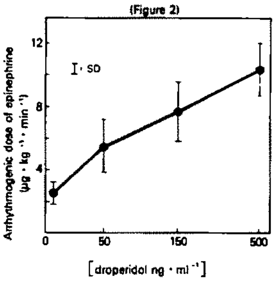
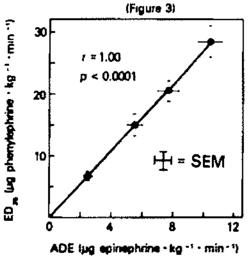
Dose-response curve of droperidol vs α_1 adrenergic responsiveness in halothane (1.5%) anesthetized dogs (n = 7)
(Figure 1)



Dose-response curve of droperidol vs epinephrine-induced arrhythmias in halothane (1.5%) anesthetized dogs (n = 7)
(Figure 2)



Relationship between arrhythmia threshold and α blockage at 4 droperidol levels in halothane (1.5%) anesthetized dogs (n = 7)
(Figure 3)



Title:

THE HEMODYNAMIC EFFECTS OF LORAZEPAM AS AN ADJUNCT TO FENTANYL/OXYGEN ANESTHESIA

Authors: *AB Hill, M.B., F.F.A.R.C.S., BJ Muller, M.D., S Samra, M.D., and M Kirsh, M.D.*

Affiliation: *Departments of Anesthesiology and Surgery - Section of Thoracic Surgery, University of Michigan Medical Center, Ann Arbor, Michigan 48109*

Introduction. *Induction of anesthesia with high dose fentanyl is a recognized technique for cardiac patients. Recently there have been reports of intraoperative awareness following fentanyl 72 μg/kg (1) and 90 μg/kg (2). It is not unusual to add an amnesic to anesthetic agents, but Stanley (3) has shown that diazepam 10 mg administered as an adjunct to fentanyl caused a decrease in stroke volume (S.V.), cardiac output (C.O.), blood pressure and systemic vascular resistance (S.V.R.), during anesthesia for mitral valve replacement. In addition Roach (4) reported a significant drop in mean arterial pressure (M.A.P.) when diazepam 0.25 mg/kg was administered prior to fentanyl anesthesia for coronary artery bypass grafting (C.A.B.G.). In view of these reports we designed the following study to investigate the hemodynamic effects of the recognized amnesic, lorazepam, during fentanyl/-oxygen anesthesia in patients undergoing C.A.B.G.*

Methods. *Twenty patients giving informed consent to the institutionally approved protocol were studied. All patients were premedicated with morphine 0.15 mg/kg and scopolamine .004 mg/kg. Prior to induction of anesthesia two peripheral I.V. lines were placed, a radial artery cannulated and a Swan-Ganz catheter floated into the pulmonary artery. The study was conducted in a double blind fashion. All patients received fentanyl 50 μg/kg and a simultaneous infusion of pancuronium 0.036 mg/kg plus metocurrine 0.144 mg/kg administered over ten minutes. Patients then received either saline 4 mls (Group A) or lorazepam .05 mg/kg (Group B) infused I.V. over five minutes.*

The trachea was then intubated and the surgical preparation commenced. Hemodynamic measurements were made prior to induction (c); after fentanyl 50 μg/kg (1); after the test drug (2); after intubation (3); just prior to (4); and after skin incision (5); and after sternotomy (6). Measured parameters included heart rate (H.R.), systolic, mean and diastolic arterial and mean pulmonary artery pressures, pulmonary capillary wedge pressure (P.C.W.P.), right atrial pressure, and cardiac output (C.O.). The following indices were computed: cardiac index (C.I.), rate pressure product (R.P.P.), and S.V.R. Data were analyzed using Student's paired t test, measurements after fentanyl were compared with subsequent measurements.

To detect differences between the groups a Student's two sample t test was utilized.

Results. *Those patient's who received lorazepam showed a significant decrease in M.A.P. before and after skin incision. H.R. decreased in Group A before skin incision and in Group B before skin incision and after sternotomy. C.I. and S.V.R. showed similar changes in each group. C.I. decreased before and after skin incision and after sternotomy. In the saline group R.P.P. decreased before skin incision and decreased before skin incision and after sternotomy in those who received lorazepam. There was no significant difference in P.C.W.P.*

The only difference between the groups was in M.A.P. prior to skin incision.

Discussion. *Awareness is an uncommon, undesirable and often unexpected complication of anesthesia. Diazepam has a short duration of action as regards amnesia but produces sustained decreases in hemodynamic values when used as an adjunct to fentanyl anesthesia. Lorazepam is a long acting amnesic which produced similar hemodynamic changes to those of saline except for an unsustained decrease in M.A.P. We therefore, conclude that lorazepam is a useful adjunct to fentanyl/oxygen anesthesia.*

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HEMODYNAMIC PARAMETERS

mean ± (S.D.)

		C	1	2	3	4	5	6
MAP	A	98(12)	92(14)	89(11)	90(10)	+84(8)	91(16)	96(15)
	B	90(13)	87(8)	82(12)	83(13)	75(8)*	81(7)	89(8)
HR	A	58(11)	63(13)	63(14)	65(13)	58(11)*	60(12)	63(13)
	B	55(7)	62(7)	61(6)	63(8)	57(5)*	68(8)	55(7)*
CI	A	2.7(.9)	2.7(.7)	2.4(.6)	2.5(.5)	2.0(.6)*	2.1(.4)*	2.1(.5)*
	B	2.5(.4)	2.7(.8)	2.5(.7)	2.5(.8)	2.2(.4)*	2.0(.3)*	2.1(.4)*
RPP	A	8353 (1990)	8520 (2367)	8520 (2264)	8595 (1838)	7295* (1862)	8291 (2099)	8837 (1926)
	B	7986 (1423)	8417 (1813)	7706 (1340)	7732 (1377)	6440* (996)	7179 (1257)	7219* (1565)
SVR	A	1446 (333)	1304 (341)	1439 (403)	1382 (176)	1560 (304)	1610 (327)	1736* (233)
	B	1438 (318)	1307 (340)	1319 (383)	1341 (460)	1314 (399)	1564 (530)	1622* (399)

* p< .05 as compared to 1
+ p< .05 between the groups

Title: 2-D ECHO STUDY OF LV MECHANICS IN CABG PATIENTS RECEIVING NITROPRUSSIDE

Authors: Z. Hillel, M.D, D. Thys, M.D., M. Goldman, M.D., B. Mindich, M.D., JA Kaplan, M.D.

Affiliation: Department of Anesthesiology, Medicine, and Surgery, Mount Sinai School of Medicine
One Gustave L. Levy Place, New York, New York 10029

Introduction. Afterload reduction with vasodilators has been used to improve cardiac output in coronary artery bypass graft (CABG) patients.[1] A previous report showed that in the absence of vasodilators, afterload increased after cardiopulmonary bypass (CPB) under fentanyl-diazepam anesthesia.[2] The present 2D echocardiographic (2DE) study of CABG patients looked at post-CPB cardiac performance under anesthesia with and without sodium nitroprusside infusion. 2DE allows assessment of left ventricular (LV) mechanics not accessible by standard monitoring techniques.

Methods. After institutional approval and informed consent were obtained, 12 patients with LV ejection fraction $(EF) > 50\%$ undergoing CABG were randomized into two equal groups, nitroprusside (N) and placebo (P). A radial artery or aortic root catheter was used to follow mean arterial pressure and systolic arterial pressure (SAP). Pulmonary capillary wedge pressure (PCWP), cardiac output, and central venous pressure were measured using a pulmonary artery catheter. 2DE data were acquired by placing a 5 MHz transducer directly on the heart and recording the short axis area (SA) at the papillary muscle level of the LV. Pre-CPB data were recorded immediately after pericardiotomy. During CPB all patients were cooled to a core-temperature of 28°C. Beginning with rewarming, an infusion of either nitroprusside or placebo was started by a "blinded" investigator and continued for 15 minutes after termination of CPB. Data were recorded at 5', 10' and 15' post-CPB. Derived 2DE parameters were end-systolic and end-diastolic area computed from the average of four sequential heart beats. Areas were converted to volumes (V) by the relation $V=(SA)^{2/3}\cdot(45+SA)/(15+SA)$ and the volumes were used to calculate LV end-systolic volume index (ESVI), LV end-diastolic volume index (EDVI) and EF. Ventricular compliance and contractility were estimated from the relationship between PCWP and EDVI and the relationship between SAP and ESVI, respectively. Unpaired T-tests and linear regression were used in data analysis with $P < .05$ being statistically significant.

Results. Mean EDVI to ESVI values were not statistically different between N and P groups at any time. Before CPB the mean EF did not differ between N and P groups; however, at 5' and 15' post-CPB mean EF values were highter in the N compared to the P group. PCWP correlated significantly with EDVI in the P group (r=.67), but not in the N group (r=.24, Fig.1). EF showed significant negative correlation with resistance (SVR) in the N group (r=.67), but not in the P group (r=.24). The linear regressions of SAP on ESVI for individual patients had a mean slope value of 17.0±4.1 in the N group, significantly higher than the corresponding value of 6.4±1.3 in the P group (mean ± SEM)($P < .02$, average value of r was .77), (Fig.2).

Discussion. Patients receiving nitroprusside at the end of CPB had higher EF than patients receiving placebo drug. This increase in EF may be explained in part by decreased afterloading as indicated by the significant negative correlation between EF and SVR. However, it may also be due to increased LV compliance and/or contractility. Increased LV compliance is suggested by failure of PCWP to increase with increasing EDVI in patients receiving nitroprusside, in contrast to placebo patients whose PCWP increased with EDVI. Increased LV contractility is suggested by the markedly steeper slope of the SAP-ESVI relationship in the N group compared to P group.[3] In summary, CABG patients with good LV function appear to have greater LV ejection fraction, LV compliance and LV contractility with nitroprusside administration post-CPB. We conclude that nitroprusside administration post-CPB during CABG under fentanyl-diazepam anesthesia may improve left ventricular performance.

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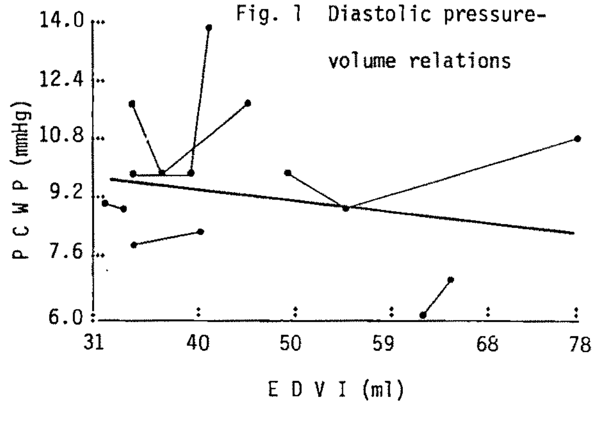

Fig. 1 Diastolic pressure-volume relations

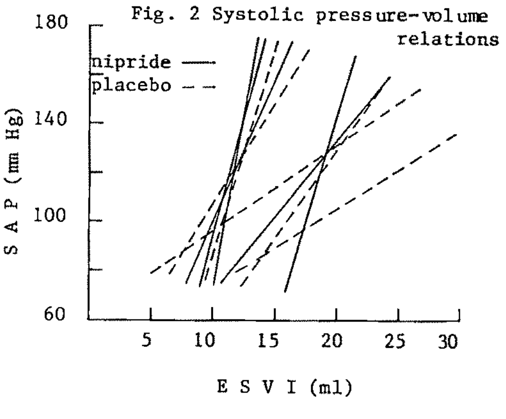

Fig. 2 Systolic pressure-volume relations

Title: PROTAMINE: DOES IT ALTER RIGHT VENTRICULAR PERFORMANCE?

Authors: RL Hines, M.D., PG Barash, M.D.

Affiliation: Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510

Introduction. The right ventricle has been identified as a target site for cardiac decompensation following protamine infusion. While many studies suggest a predominant vasodilator action, a recent report implies a primary increase in pulmonary vasoconstriction (following protamine) leading to RV failure (1,2). To determine if changes in RV performance occur on episodic or a reproducible basis, we evaluated both right and left ventricular function in patients receiving protamine infusion.

Methods. Utilizing a protocol approved by the Human Investigation Committee, twenty (N=20) patients (mean age 64 ± 1.1 SEM) scheduled to undergo CABG (N=11), valve replacement (N=7) and combined valve and CABG (N=2) were evaluated. Following premedication with morphine (0.1 mg/kg) and scopolamine (0.4 gm), intravascular catheters were placed percutaneously under local anesthesia. Induction was performed with fentanyl (50 mg/kg), and pancuronium (0.1 mg/kg) was utilized for muscle relaxation. Ventilation was maintained using an $F_IO_2 = 1.0$. Hemodynamic measurements were recorded at end exhalation for the following events: pre-protamine infusion, 1/2 total protamine infusion, completion of protamine infusion and sternal closure. Measured variables included: right ventricular ejection fraction (RVEF), heart rate (HR), blood pressure (BP), right ventricular pressure (RVEDP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output. Protamine dose was calculated to reverse residual heparin as measured by the activated clotting time (ACT) (mean dose 504 mg ± 5.3 SEM). Duration of protamine infusion was also recorded (mean 18.5 min ± 1.4 SEM). Data are expressed as mean ± SEM. Statistical evaluation was performed by one way analysis of variance, $p < 0.05$ was considered significant.

Results. (Table). There were no significant changes from control (pre-protamine) values in CI, BP, RVEDP, PVRI or SVRI during or after protamine administration. No statistically significant differences could be found in the cardiovascular response to protamine within high risk subsets of our patient population.

Table
(N = 20)
Mean ± SEM

	Pre-Prot	1/2 Prot	Total Prot	Pre-sternal Closure
RVEF	35±1.3	35±1.1	35±1.1	35±1.3
RVEDP	7±0.8	8±0.8	7±0.8	8±0.8
HR	87±3.4	85±2.8	85±3.1	85±3.0
BP	79±3.2	81±2.8	82±2.9	88±3.2
PAP	23±1.7	23±1.7	23±1.8	23±2.1
PCWP	14±1.2	14±1.3	14±1.3	14±1.1
CI	3.5±.1	3.4±.2	3.4±.1	3.5±.1
PVRI	2.6±1.1	2.8±1.3	2.9±1.3	2.7±1.2
SVRI	20±1.2	22±1.4	22±1.2	23±1.4

RVEF(%) = right ventricular ejection fraction; RVEDP = right ventricular end diastolic pressure (mmHg); HR = heart rate (beats/min); MBP = mean blood pressure (mmHg); PAP = mean pulmonary artery pressure (mmHg); CI = cardiac index (L·min·m^{-2}); SVRI = systemic vascular resistance index (RU·m^{-2}); PVRI = pulmonary vascular resistance (RU·m^{-2})

Discussion. Our data suggests that protamine does not exert a significant effect on right ventricular function on a consistent basis. The episodic RV failure previously reported following protamine may be hypothesized to occur on the basis of anaphylaxis or activation of the complement cascade. Precise measurement of right ventricular performance during and following protamine infusion failed to reveal any predictable deterioration in right ventricular function in a group of high risk patients. In conclusion, right ventricular failure is not a reproducible sequela following protamine administration.

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Title: Serum Inorganic Fluoride Post-Enflurane in Children

Author: A. J. Hinkle, M. D.

Affiliation: Department of Surgery (Anes.) and Maternal and Child Health, Dartmouth-Hitchcock
Medical Center, Hanover, New Hampshire 03756

Introduction. Recently, investigators have been advocating the use of enflurane over halothane anesthesia in children because of a greater stability in cardiac rhythm.[1] The biotransformation of enflurane anesthesia has been clearly shown to induce inorganic fluoride nephrotoxicity. Mazze has suggested a nephrotoxic threshold between 21 to 33 uM/L.[2]

It is unknown to what extent serum inorganic fluoride is elevated after enflurane anesthesia in children. Since renal maturation is not complete in children until one year of age, this population of patients could be at a higher risk for inorganic fluoride nephrotoxicity.[3] This study defines serum inorganic fluoride levels after enflurane anesthesia in children over one year of age.

Method. Eight male children age 1-9 years (mean 5 years) were studied after obtaining informed consent and approval by our Committee for the Protection of Human Subjects. All children were healthy, ASA1 patients who had no recent anesthetic experience.

Anesthesia was induced with either rectal methohexital (25 mg/Kg) or intravenous pentothal (4 mg/Kg) and a 70% N_2O/30% O_2 mixture. Baseline serum Fl- levels were drawn. Once anesthetized all patients were given succinylcholine for intubation and allowed to breath spontaneously. An indwelling heparinized venous catheter was inserted.

Blood was samples at 1, 3 and 6 hours after the discontinuation of enflurane anesthesia. Serum samples for fluoride were frozen (-70°C) until analyzed and then measured together (Orion model 94-09 Fluoride Electrode).[4]

Results. Serum inorganic fluoride levels at 0, 1, 3 and 6 hours post-enflurane are found in Table 1. The peak Fl- levels occurred at 1 hours post-enflurane with a mean of 10.5 uM/L (range 6.85-14.5 uM/L Figure 1). There did seemto be a relationship between age and peak serum Fl- levels such that the younger the child the higher the peak Fl- level.

Discussion. There are several observations to be made in this study. First the peak serum Fl- level occurred earlier in children than in the adult (at 1 hr. vs 3-4 hrs.). In addition the mean peak Fl- level was lower than that value previously described for adults (10.5 uM/L vs 17 uM/L). The earlier and lower peak serum Fl- level may be explainable because of slower enflurane metabolism, increased renal clearance of Fl-, greater Fl- deposition in bone or a more rapid enflurane elimination at the conclusion of anesthesia. When investigators looked at the biotransformation of halothane in children they also found earlier and smaller peak serum bromide levels as compared to the adult also suggesting less biotransformation.[5]

The apparent relationship between age and peak serum Fl- levels is more difficult to explain. If one assumes that the younger a child the more unable they are to biotransform an inhaltional agent one would expect opposite findings (i.e. lower peak serum Fl- levels in the younger child. The higher peak serum Fl- levels in the younger child suggests another factor other than biotransformation. We know that the younger a child the smaller their muscle and fat groups.[6] With anesthetic administration times of 1.5-2.5 hours it may be that the smaller muscle group in the younger child reduces the volume of distribution of the anesthetic resulting in an overall higher peak serum Fl- level in these younger patients.

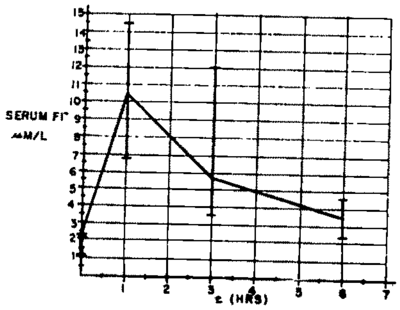
We can certainly conclude that in children 1-9 years of age, serum Fl- levels after enflurane anesthesia are below the adult nephrotoxic range of 20-30 uM/L.

TABLE 1 SERUM Fl- (uM/L)

Age (yrs.)	0	1 hr	3 hr	6 hr
1	2.35	14.5	5.5	4.5
2	2.1	13.0	4.5	2.5
3	2.0	14.0	12.0	4.4
5	1.6	10.5	6.0	3.0
6	1.8	8.5	3.5	2.3
7	1.3	6.85	5.5	4.0
8	1.15	12.0	4.0	3.5
9	1.3	4.4	3.55	2.5

FIGURE 1

Serum Fl- post-enflurane in children



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Title: CARDIOVASCULAR AND ELECTROENCEPHALOGRAPHIC EFFECTS OF LAUDANOSINE IN "NEPHRECTOMIZED" CATS

Authors: MD Ingram, M.D., RJ Sclabassi, Ph.D., M.D., RL Stiller, Ph.D., DR Cook, M.D. and
MH Bennett, Ph.D.

Affiliation: Departments of Anesthesiology, Neurological Surgery and Psychiatry,
University of Pittsburgh School of Medicine, Pittsburgh, PA 15261

Introduction. Atracurium, a new nondepolarizing muscle relaxant, spontaneously decomposes (Hofmann elimination) and is metabolized by nonspecific esterases. An end-product of both these pathways is laudanosine, a monoquarternary amine that is renally excreted. Laudanosine has been associated with seizure-like activity in dogs at high doses (10-12 mg/kg) (1). Laudanosine is detectable in the plasma of patients following atracurium bolus injection and/or infusion. There are concerns whether laudanosine accumulation and toxicity may occur in the anephric patient following atracurium bolus and/or infusion.

Methods. Six healty cats of either sex weighing between 2.0 and 2.6 kg were studied. Anesthesia was induced with IV thiopental (25 mg/kg), the cat was intubated, and anesthesia maintained with halothane (0.5 to 1.2%) in air. Pancuronium (0.1 mg/kg) or gallamine (4 mg/kg) was used to facilitate surgical preparation and mechanical ventilation. $PaCO_2$ was maintained between 35-40 torr. A femoral arterial catheter was inserted and the ureters ligated. Scalp leads or screws in the boney skull (using an analogous 10-20 configuration) provided input for four EEG channels and spectral analysis. Arterial pressure, EKG (lead I), and right hemisphere EEG were continuously displayed and recorded on a multichannel recorder. EEG data for spectral analysis were collected and amplified with a Grass Model 12 neurodata system with appropriate filters. Data were collected during 2 second epochs with 30 second interepoch intervals, 5 epochs per group. Raw EEG data were stored in a computer file. Power spectra of all four channels were calculated and displayed on-line.

Following control measurements, laudanosine (2 mg/kg) was administered. Five minutes following the bolus an infusion of laudanosine at 15 μg/kg/min was instituted. At successive 30 minute intervals the infusion rate was increased to 30, 60 and 120 μg/kg/min, respectively. Following the 120 μg/kg/min period laudanosine was infused at the maximum rate of the infusion pump (99 ml/hr) for an additional 30 min or until the infusate was expended. These flow rates varied between 1030-1360 μg/kg/min. Continuous physiologic measurements were recorded during the control period and throughout the infusion protocol. EEG/power spectra were collected at baseline and every 15 minutes during the infusion protocol. Blood and CSF were collected at the end of the experiment. Laudanosine plasma and CSF concentrations were measured with a sensitive, specific HPLC assay.

Results. Laudanosine plasma concentrations 5 minutes post-bolus were 3.1 μg/ml ± 0.5 SEM with a decrease in concentration during the first 30 minutes of infusion. Thereafter there was a progressive increase over the remaining infusion periods (Table). All cats demonstrated transient ventricular arrhythmias and a decrease in mean arterial pressure (MAP) following the laudanosine bolus. The EEG and power spectra were unchanged at infusion rates of up to 60 μg/kg/min (mean plasma laudanosine 4.4 μg/ml). Above 60 μg/kg/min, in spite of cardiovascular stability, the EEG showed periodic delta wave activity separated by periods of suppression and low amplitude beta wave activity. Higher infusion rates increased the degree of suppression. These EEG changes were reflected in the power spectra of all four channels. No epileptiform activity was noted at these infusion rates.

At the maximum infusion rate (1030-1360 μg/kg/min), ventricular irritability and profound hypotension developed. Additionally the animals developed complete amplitude suppression intermixed with some spiking activity. Spinal cord release motor activity (twitching) was also seen in 3 of 6 cats.

Discussion. Atracurium can be given by either bolus or continuous infusion. Atracurium infusion rates of 5-15 μg/kg/min (with resulting plasma laudanosine concentrations of 400-600 ng/ml) are required to maintain neuromuscular blockade during various anesthetics. Laudanosine is an end-product of atracurium metabolism; in theory, two molecules of laudanosine can be generated from each molecule of atracurium. A laudanosine bolus followed by an infusion was given to simulate clinical conditions. These laudanosine bolus and infusion rates (in theory) represent 1 mg/kg atracurium and atracurium infusion rates of 7.5, 15, 30, and 60 μg/kg/min, respectively. Our data demonstrate that laudanosine can cross the blood-brain barrier. At plasma laudanosine concentrations greater than 4.4 μg/kg the described EEG and power spectra changes occurred. These plasma laudanosine concentrations are at least 10-fold higher than those noted in patients.

At plasma concentrations greater than 7.9 μg/ml profound hypotension and EEG suppression with occassional spikes occurred. The mechanisms for the cardiovascular depression and EEG suppression are unclear, but the latter may be related to the low perfusion pressure. The twitching is most likely due to spinal cord release. Grand-mal seizures reported in dogs may represent a species difference. Whether laudanosine concentrations high enough to produce adverse EEG effects can be achieved in anephric patients following atracurium is unknown; however, these data suggest that it is unlikely.

Table. Laudanosine Concentrations Following 30 Minute Infusion at Indicated Rates

Infusion Rate (μg/kg/min)	Laudanosine (μg/ml)
15	2.3 ± 0.7
30	3.2 ± 0.7
60	4.4 ± 1.2
120	7.9 ± 1.7

Reference.

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Title: COMPARISON OF THIOPENTAL-NITROUS OXIDE-HALOTHANE WITH KETAMINE-OXYGEN-HALOTHANE AS ANESTHETIC AGENTS FOR CESAREAN SECTION

Authors: Jones MM, Joyce TH, Adenwala J, Mawji F.

Affilia: Department of Anesthesiology-Baylor College of Medicine, Houston, Texas 77030 USA

Introduction. Ketamine-halothane-oxygen has potential advantages as an anesthetic combination for cesarean section. Since ketamine in contrast to thiopental is a powerful analgesic, nitrous oxide is not necessary as a carrier gas. With more oxygen available, the fetus should be better oxygenated at birth. Animal studies have indicated that ketamine can increase uterine artery perfusion. These factors should be reflected in better umbilical blood gases as well as higher Apgar and neurobehavioral scores.

Methods. After approval from the Human Research Committee and patient consent, fifty patients undergoing general anesthesia for elective cesarean section were assigned to one of two groups. The thiopental group (25) was induced with thiopental (3mg/kg), and anesthesia maintained with 4L of N_2O and 4L of O_2 with 0.5% halothane until delivery of the baby. The ketamine group (25) was induced with ketamine (1mg/kg), maintained with a ketamine infusion delivering 50mcg/kg/min, with 0.5% halothane and 99.5% O_2 until delivery of the baby. After delivery of the baby, 10mg of diazepam was given to all patients. The patients were then maintained with fentanyl or morphine as needed until the end of the operation. Blood gases were obtained at birth from the maternal artery and umbilical artery and vein. Apgar scores were obtained at 1 and 5 minutes and Early Neonatal Neurobehavioral Score done at 2-4 hours and 24-36 hours after birth. A maternal interview with questions designed to reveal awareness during anesthesia and dreams was performed.

Results. Final statistics after completion of the 50 patients are pending. Preliminary statistics after 36 patients (thiopental 19 patients, ketamine 17 patients) revealed that the two groups were similar in demography. Maternal arterial blood gas values revealed a higher mean pO_2 (318±147 torr) in the ketamine group than in the pentothal group (194±79 torr). A small difference in ventilation between the groups (pCO_2: Ketamine - 38±5.0 torr, pentothal - 31±5.4 torr) was reflected in the pH (ketamine - 7.38±.06, pentothal - 7.42±.06). Umbilical arterial and venous blood gas values, time to sustained respiration, and Apgar scores between the two groups were not significantly different when compared using the Student's t-test at the 95% confidence level. The 2-4 hour ENNS revealed a slight prolongation in the average decrement response to Moro, light and sound reflexes in the ketamine group with only the light reflex decrement remaining prolonged at 24 hours. When comparing the mean ENNS scores in each category, the only statistically significant difference occurred in the sucking reflex at 2-4 hours with the ketamine group scoring slightly higher. Dreaming occurred in four patients in the ketamine group; no patients in the pentothal group reported dreaming.

Discussion. This study appears to differ from the 1978 report by Hodgkinson[1] which suggested ketamine resulted in better ENNS Scores than thiopental when used as an induction agent. Despite the theoretical advantages, no significant improvement in the Apgar Scores or UA and UV gases were noted in the preliminary statistics. Except for the light reflex, the prolongation in decrement response had resolved by the 24 hour exam. This ketamine technique would allow the administration of a high inspired O_2 concentration to those parturients requiring it and the higher maternal pO_2 could potentially be helpful in an asphyxiated high risk infant. Also, avoiding the use of N_2O would eliminate the risk of methionine synthetase inhibition proposed by Eger.

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Title: MASK INDUCTION RESPONSES TO A PRE-DETERMINED TECHNIQUE AND RECOVERY CHARACTERISTICS OF ISOFLURANE ANESTHESIA IN CHILDREN

Authors: M.M. Joseph, M.D., K.K. Win, M.D., D.H. Nelson, M.D., D.L. Warner, M.D., and S.N. Steen, Sc.D., M.D.

Affiliation: Department of Anesthesiology, University of Southern California - Los Angeles County Medical Center, Los Angeles, California 90033.

Introduction. Isoflurane anesthesia in children has been reported to produce a high incidence of airway problems (1) and a longer induction time compared to halothane (2). Our clinical impressions in over 1,500 children who received isoflurane (July 1981 to date) did not accord with these findings (3,4,5). Accordingly, we re-assessed the incidence the effects of isoflurane when administered to children.

Methods. We studied 66 children (1-12 years), ASA I or II, scheduled for elective surgery. Premedication consisted of atropine alone (A) or with meperidine and hydroxyzine (B); group C consisted of no premedication. Following mask induction with $N_2O:O_2$ at 7:3 l/min for 30 sec (using a semi-closed anesthetic circuit), isoflurane was added in 0.25% increments at 30-sec intervals during spontaneous respirations until loss of lid reflex, presence of regular respirations and absence of purposeless movements; following which, isoflurane was maintained at the highest concentration required with the $N_2O:O_2$ mixture being decreased to 3:2 l/min. An intravenous cannula was then inserted. Orotracheal intubation was performed when indicated. At the end of anesthesia, times for return of reflexes were recorded, and in the PAR the children were evaluated using the recovery score devised by Steward (6). Complications were recorded - using the isoflurane evaluation form of the 1982 multicenter clinical study (8).

Results. The times for loss of responses during induction, and the placement of the intravenous cannula, and incision with the corresponding anesthetic concentrations of isoflurane are listed in Table 1. The occurrence of reflex actions are presented in Table 2.

Discussion. Using a fixed-incremental and timed administration for inspired isoflurane to children, we observed that the times for loss of responses were less than previously recorded (6). For all the groups, the corresponding data for the isoflurane concentrations were also lower than those reported elsewhere (1,10). Of the reflex actions noted (Table 2) the incidence of airway problems, movement and excitement were similar to those reported in the New Drug Application for adults (9) but less than those reported by Frieson and Lichtor in children (1). The findings substantiate our previously reported clinical impressions that isoflurane produces a relatively rapid induction with a low incidence of reflex actions in children that in no instance required discontinuance of the agent.

TABLE 1. RESPONSE TIMES ($\bar{X}$ ± SEM) AND ISOFLURANE CONCENTRATIONS

	A (N=26)	B (N=28)	C (N=12)
Lid Reflex[a]	3'10" ± 15"	2'56" ± 12"	3'15" ± 14"
Movement[b]	3'37" ± 15"	3'07" ± 22"	3'17" ± 18"
Respiration[c]	3'45" ± 20"	3'12 ± 1'15"	3'00" ± 23"
IV Placement	7'49" ± 45"	4'48" ± 15"	6'28" ± 40"
% Isoflurane	1.7 ± 0.1	1.4 ± 0.1	1.6 ± 0.1
Incision	25'42" ± 3'24"	18'16" ± 1'23"	19'45" ± 1'31"
% Isoflurane	1.6 ± 0.1	1.8 ± 0.1	1.9 ± 0.1

[a] loss [b] absence (purposeless) [c] presence (regular)

TABLE 2. REFLEX ACTIONS

	A (N=26)	B (N=28)	C (N=12)
Breath-holding	1	0	0
Secretions	1	1	0
Coughing	3	1	0
Laryngospasm	2	3	0
Hiccough	1	0	1
Movement	2	1	0
Excitement	0	1	0
Vomiting	0	0	1

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Title: SHIVERING AND CHANGES IN MIXED VENOUS OXYGEN SATURATION AFTER CARDIAC SURGERY

Authors: J.A. Kaplan, M.D. and A.V. Guffin, MMS

Affiliation: Department of Anesthesiology, Mount Sinai School of Medicine, One Gustave L. Levy Place,
New York, New York 10029

Introduction. Shivering is commonly seen following anesthesia and surgery. Violent muscle activity often occurs, causing an increased metabolic demand for oxygen, sometimes accompanied by simultaneous elevation in carbon dioxide and production of lactic acid. Oxygen consumption may increase as much as 600%, and the normal person compensates for this by increasing cardiac output (CO) by 3-5 times.[1] However, patients with comprised cardiac function may not be able to increase their CO; and, therefore, may attempt to compensate for the increased oxygen demand by excessive desaturation of the mixed venous blood. The purposes of this study were: 1. To evaluate the use of continuous mixed venous oxygen saturation (SvO_2) monitoring during rewarming in the postoperative period, and 2. To determine the effectiveness of therapeutic interventions in decreasing shivering and improving SvO_2.

Methods. Seven patients undergoing elective coronary artery bypass surgery with good left ventricular function (EF=49 ± 15%) were studied in the immediate postoperative period.* All patients had anesthesia induced with fentanyl or morphine and maintained with an inhalational agent, nitrous oxide/oxygen, and pancuronium. Monitors included radial and Opticath pulmonary arterial catheters, and electrocardiographic leads II and V_5. A bubble oxygenator, systemic hypothermia (28°C), and cold, potassium cardioplegia were used, and all patients were rewarmed to an esophageal temperature of 37°C. In the intensive care unit (ICU), SvO_2 was recorded continuously, and hemodynamics, arterial and venous blood gases, hemoglobin, and body temperature were measured. The $A\text{-}VO_2$ difference, oxygen consumption, and oxygen delivery were calculated from standard formulae. Shivering was graded on a scale of 0-4, with 0=no shivering, and 4=continuous violent muscle activity. Treatment was initiated when shivering increased to grade 4, or when SvO_2 declined by 1/3 of its value on arrival in the ICU. Patients were treated in a serial manner, with 25-50 mg of meperidine or 5-10 mg of morphine. Failure to achieve significant improvement in shivering resulted in the administration of the other narcotic. If shivering still persisted, pancuronium was given. Statistical analysis of the data was performed using Students paired T-test with $P < .05$ being significant, and a linear regression analysis.

Results. SvO_2 decreased from control in all patients as the degree and duration of shivering increased (Table). Two of 7 patients showed an initial increase in CO in an attempt to compensate for the increased oxygen demand, but the remaining 5 patients demonstrated no change or a decrease in CO. During shivering, oxygen consumption doubled, oxygen delivery remained unchanged, and one patient developed mild metabolic acidosis. The decreased SvO_2 correlated with the shivering and increased oxygen consumption (r=0.85). Morphine was ineffective in reducing shivering or increasing SvO_2. However, 5 of 7 patients had a reduction in shivering and increased SvO_2 with meperidine. Two patients required pancuronium to stop the shivering and return SvO_2 to acceptable limits.

Discussion. Shivering produces increased oxygen consumption and a demand for increased CO. However, in these patients after hemodilution and cardiopulmonary bypass, CO and oxygen delivery remained low. Even with myocardial revascularization, they were unable to increase cardiac function and CO in the immediate postoperative period. The SvO_2 measurement correlated well with oxygen consumption changes, but did not reflect CO changes. This contrasts with data reported in anesthetized, paralyzed patients during surgery where oxygen consumption was relatively constant and SvO_2 correlated with changes in CO.[2]

Various drugs have been used to control shivering in order to optimize the oxygen delivery/consumption ratio. Muscle relaxants alleviate shivering, but may not be desirable in the awakening patient. Claybon and Hirsh previously showed that meperidine could be used to control postoperative shivering and that it did not reoccur within 45 minutes in 68% of patients studied.[3] This study confirms their findings and suggests that meperidine may be a good alternative to muscle relaxants in the treatment of shivering.

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*This study was approved by The Institutional Research Administrative Committee.

TABLE

PARAMETER	CONTROL	SHIVERING	POST-TREATMENT
SvO_2%	73.6±4.5+	53.1±11.1*	66.0±11.0
CO (l/min)	4.8±.2	4.7±1.5	4.5±.4
$A\text{-}VO_2$ Diff (Vol%)	3.3±.5	6.4±2.2*	4.5±1.3
O_2 Consump(ml O_2/min)	154±27	298±151*	195±38
O_2 Delivery(ml O_2/min)	607±82	621±239	604±119
Temperature (°C)	33.8±.6	34.5±.3	34.8±.5
Shivering Score	1.2±1.1	2.9±.6*	0.4±.1
Hemoglobin (mg%)	9.8±1.7	10.0±1.6	9.9±1.6

*$P < .05$ compared with control
+(x±SD)

Title: INFLUENCE OF DILTIAZEM ON MYOCARDIAL METABOLISM AND CORONARY HEMODYNAMICS DURING ISOFLURANE ANESTHESIA IN THE DOG

Authors: PA Kapur, M.D., SE Tippit, B.S., and J.H. Campos, M.D.

Affiliation: Department of Anesthesiology, University of California, Los Angeles, California 90024

Introduction. Diltiazem (D) has been reported to alter coronary blood flow (CBF), as well as improve the distribution of blood from subepicardial to subendocardial layers of the myocardium. Additional myocardial benefits of D may result from reduced myocardial oxygen consumption (MVO_2), and blunting of the blood flow maldistribution that occurs during the reactive hyperemia which follows an ischemic stimulus.[1,2] Isoflurane (F) however, resulted in coronary vasodilation without alteration of CBF and indirect evidence of regional ischemia was observed in patients with ischemic heart disease.[3] This study was designed to investigate effects of four plasma levels of D on CBF and myocardial metabolism in the intact dog in the presence of anesthetic levels of F.

Methods. 15 dogs (23±1 kg) were anesthetized with F (1.49–1.54% end tidal) in 40% O_2 in air. Femoral venous and arterial catheters were placed for fluid administration and measurement of phasic and mean arterial blood pressure (MAP). A pulmonary artery (PA) catheter for right atrial (RA) and PA occluded (PAO) pressures, a micromanometer tipped catheter for left ventricular pressure and derivation of LV dP/dt, and a Webster thermodilution coronary sinus catheter were introduced, aided by fluoroscopy. The ECG was recorded at fast paper speed for measurement of PR intervals. Cardiac outputs were by the Fick method. Total CBF was measured in duplicate by thermodilution; coronary and systemic vascular resistance (CVR, SVR), and cardiac index (CI) were calculated. Normocarbia and normothermia were maintained. Arterial, mixed venous, and coronary sinus (cs) samples were simultaneously obtained for blood gases and oxygen content, as well as arterial and cs samples for lactate, D, and plasma epinephrine (E) and norepinephrine (NE) levels. Blood sample losses were replaced. MVO_2 and myocardial lactate extraction ratio (MLE) were computed. Following hemodynamic stabilization for 2h on F and measurement of control values, each dog received two of the following boluses and 30 min infusions of D in increasing order: 100µg/kg +4µg/kg/min; 200µg/kg + 8µg/kg/min; 300µg/kg + 12µg/kg/min; 400µg/kg + 20µg/kg/min. Cardiovascular measurements and plasma samples were taken after the bolus and at 20 and 30 min of infusion. The data were evaluated using analysis of variance for repeated measures with Bonferroni t-tests. P<0.05 was considered significant.

Results. Experimental results were sorted into 4 groups by plasma D levels at intervals of 100 ng/ml, resulting in mean plasma D levels of I: 47±3; II: 148±12; III: 263±10; and IV: 379±43 ng/ml. There were no differences between the 20 and 30 min values during the infusions of D. Control hemodynamic values were similar for the 4 groups and showed no change compared to the steady state D levels achieved in this study, except for a decreased LV dP/dt and increased PAO and RA at the higher levels of D. Values for group IV are shown in table 1. Values for CBF, CVR, MLE, and MVO_2 are shown in table 2. No changes were observed. PR interval of the ECG was significantly and progressively prolonged (table 2) with increasing plasma levels of D up to and including third degree heart block in several animals.

Discussion. In the presence of 1.5% end tidal F, the imposition of the plasma levels of D achieved in this study resulted in no significant change in global myocardial metabolism or coronary hemodynamics in animals with presumed normal coronary anatomy. Further studies are now indicated to evaluate the combined local effects of D and F in ischemic compared to normal regions of myocardium, to determine whether D can mitigate the preferential redistribution of blood flow to normal regions attributed to F.[3] Despite the lack of major systemic or global coronary effects of these levels of D during F and concomitant lack of change of plasma E and NE, atrioventricular conduction interfering properties of D were prominent.

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Table 1. Group IV

	HR (bpm)	MAP (mmHg)	RA (mmHg)	PAO (mmHg)	LV dP/dt (mmHg/s)
C	127±4	91±5	6±1	8±1	1966±133
30 min	112±6	87±5	9±1*	12±1*	1600±110*

	CI (l/min)	SVR (dynes/s/cm^{-5})	E (pg/ml)	NE (pg/ml)
C	4.43±0.48	1754±243	262±63	134±48
30 min	4.24±0.40	1577±147	350±134	223±58

Mean ± SEM; * $p < 0.05$ compared to control

Table 2.

	Group	n	Control	30 Min
CBF (ml/min)	I	5	105±15	100±12
	II	7	164±21	168±29
	III	7	126±19	133±9
	IV	7	178±30	159±33
CVR (mmHg·min)/ml	I	5	0.65±0.10	0.65±0.12
	II	6	0.47±0.07	0.51±0.11
	III	7	0.56±0.10	0.48±0.05
	IV	6	0.46±0.11	0.48±0.13
MLE (%)	I	6	0.39±0.05	0.31±0.04
	II	7	0.41±0.07	0.32±0.04
	III	7	0.33±0.05	0.25±0.05
	IV	7	0.28±0.04	0.25±0.03
MVO_2 (ml/min)	I	6	6.1±1.3	6.5±0.5
	II	5	13.5±2.1	12.0±2.2
	III	5	7.8±1.0	8.9±0.3
	IV	7	12.5±2.4	12.0±2.2
PR interval (ms)	I	7	104±6	114±7 *
	II	8	102±5	125±10*
	III	8	113±7 †	143±24††
	IV	8	128±9 †	156±10††

Mean ± SEM: * $p < 0.05$ compared to control
† 2nd of 2 doses; D levels: III=87±16; IV=138±30ng/ml
†† junctional rhythms in 1/8 (III) and 2/8 (IV) dogs

Title: INCOMPETENCY OF UNIDIRECTIONAL DOME VALVES: A MULTI-HOSPITAL STUDY

Authors: JM Kim, M.D., AL Kovac, M.D., and HS Mathewson, M.D.
Affiliation: Department of Anesthesiology, University of Kansas College of Health Sciences and Hospital, Kansas City, Kansas

Introduction. Serious intraoperative hypercarbia developed in two pediatric patients at our hospital caused by incompetent inhalation unidirectional dome valves (IUDVs). These two machines had been in active clinical service, mainly for adult patients, without apparent problems. Following those two cases, a spot check of the unidirectional dome valves (UDVs) revealed some degree of incompetency in 6 of 30 machines in our hospital. These findings prompted us to develop a simple and sensitive method testing UDV competency, and to initiate this mail survey.

Method. Competency of the UDVs were tested by anesthesiologists, nurse anesthetists, or anesthesia equipment managers who were known to one of the authors. The following is the protocol that was sent to each prospective correspondent:
(A) Preparation; remove breathing tubes from the circle, turn off all gas flows, and close pop-off valve.
(B) Checking Inhalation UDV; 1) connect a reservoir bag at the usual bag connector site and one limb of corrugated tubing on the inhalation outlet. 2) while the exhalation inlet is closed with the palm of the hand, apply positive pressure (approximately 5 to 10 cmH$_2$O) with "GENTLE SLOW BLOW" via the corrugated tubing. Filling of the reservoir bag indicates an incompetent IUDV.
(C) Checking Exhalation UDV; 1) connect a reservoir bag to the exhalation inlet and one limb of corrugated tubing on the bag connector site. 2) while the inhalation outlet is closed with the palm of the hand, apply gentle positive pressure as described in 2) above. Filling of the reservoir bag indicates an incompetent EUDV.

Results. A total of 302 anesthesia machines were surveyed among 28 hospitals of various sizes. No incompetent valves were found in 11 hospitals. Either one or both valves were found to be incompetent in 61 machines among the 17 remaining hospitals. The results are summarized in the table.

Incompetent UDVs Found in Different Types of Anesthesia Machines

Incomp UDVs	Ohio N=178	Foregger N=71	Dräger N=46	Others N=7	Total N=302
Inhal	16	6	3	1	26
Exhal	9	9	0	2	20
Both	9	4	2	0	15
Total	34	19	5	3	61
%	19	27	10	43	20

Discussion. Warping of the disk valve is the most common cause of the incompetency. Another possible cause is minor irregularity on the sharp rim of the tubular structures where the valves are seated. Valves made of malleable material (Ohio and Foregger) are highly susceptible to warping by either mechanical forces or natural deterioration. Signs suggestive of an incompetent UDV are lacking. Tidal volume delivered to the patient is not altered by the incompetent UDV, but the VD/VT ratio will be increased, due to rebreathing of expired gases. The rise in VD/VT ratio will depend upon the degree of incompetency and upon the respiratory pattern. The small tidal volumes and rapid respiratory rates, commonly seen in anesthetized children and in spontaneously breathing adults, will greatly increase the VD/VT ratio. Large tidal volumes with slow rates partially antagonize the increase in VD/VT ratio. Therefore, the degree of carbon dioxide retention caused by an incompetent UDV will be variable. Thus, the incompetent UDV may go undetected until serious hypercarbia develops in the vulnerable patient.
The principle of our method testing incompetent UDV is the demonstration of airflow against the direction of the valve when a near normal physiologic airway pressure is applied in the closed circle system. Minor warping on the valve could be corrected by applying a high pressure against the warped valve (40 cmH$_2$O positive pressure applied for similar test which was recently suggested by the Foregger Company[1]. Such a high pressure is not only beyond the normal physiologic airway pressure but also could cause a false negative result).
Recently two cases of incompetent UDVs have been reported after being detected by the mass spectrometer[2,3]. An in-line carbon dioxide analyser would also be helpful to detect hypercarbia.
In conclusion, we found that 20% of anesthesia machines in active clinical service could potentially threaten the well-being of anesthetized patients, because of defective UDVs. We feel that testing of the competency of UDVs should be included in a routine preanesthesia checkout procedure, and that an incompetent UDV should be considered in the differential diagnosis when hypercarbia occurs during anesthesia.

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Title: EFFECT OF ESMOLOL ON TACHYCARDIA INDUCED BY ENDOTRACHEAL INTUBATION

Authors: GM Korenaga, M.D., A Kirkpatrick, M.D., Ph.D., JG Lord, D.O., E Barabas, D.D.S.,
AP Winnie, M.D., and EK Zsigmond, M.D.

Affiliation: Department of Anesthesia, University of Illinois College of Medicine at Chicago, Chicago, IL 60612

Introduction. Intubation has been long known to be associated with sympathetic stimulation leading to tachycardia, hypertension, ischemic changes and other undesirable myocardial effects. Since the myocardium is more taxed by tachycardia than hypertension, a cardioselective, β-blocker with an ultrashort half-life would be ideal in managing intubation-induced tachycardia (1,2). Furthermore, since the thiopental-succinylcholine induction technique is the most common method used to induce patients for anesthesia, we felt that it was important to evaluate the effectiveness of esmolol (methyl 3-|4-(2-hydroxy-3-|isopropylamino|propoxy)phenyl| propionate hydrochloride) in attenuating tachycardia caused by intubation, utilizing this induction technique.

Methods. Following approval of the Institutional Review Board, 22 patients who gave informed written consent in ASA physical state I-III were studied. Patients on α- or β-blockers or agonists were excluded from the study. No manipulation, surgical stimulation or positioning was allowed until 5 minutes after the end of esmolol infusion. 12 patients received an infusion of 500 μg/kg/min esmolol loading dose for 4 minutes before induction with thiopental and 300 μg/kg/min for maintenance for 6 additional minutes during endotracheal intubation. The control patients (N=10) received 5% D/W infusion in place of esmolol with an infusion pump. The patients received 1.5 mg/kg hydroxyzine, 1.5 mg/kg meperidine and 3.0 μg/kg glycopyrrolate i.m. 90 minutes before anesthesia. Patients were induced with sodium thiopental at minute 4 of the esmolol infusion. 75 mg doses were given until the disappearance of lid-reflex. Succinylcholine, 1.0 mg/kg i.v. was used to facilitate endotracheal intubation. As soon as relaxation was complete, laryngoscopy was initiated. The mean duration of laryngoscopy approximated 30 seconds in each group. After the completion of intubation, nitrous-oxide/oxygen = 3:2L/min with 0.5-1.2% enflurane was administered. Blood samples were taken for plasma free-norepinephrine (NE), epinephrine and dopamine levels at the beginning of esmolol infusion, at the time of thiopental induction, 3 minutes after endotracheal-tube placement and 30 minutes after the end of infusion. Direct arterial pressure and ECG strips were continuously recorded for 5 minutes before and 30 minutes after esmolol infusion.

Results. The mean ± S.E. of heart rates in the esmolol group were 83.3 ± 5.0 beats/min before esmolol (A), 70.3 ± 4.3 before thiopental, after 4 minutes esmolol infusion (B), 85.5 ± 3.8, 3 minutes after placement of the tube (C), 86.2 ± 3.5, 5 minutes after the placement of the tube (D), and 79.5 ± 3.8 at 5 minutes after the end of esmolol infusion (E). None of these changes were significantly different from the pre-esmolol infusion values. The corresponding pulse rates for the controls were: 85.2 ± 4.3, 92.6 ± 4.6, 111.3 ± 4.4, 111.0 ± 4.8, 97.6 ± 4.2 beats/min. The heart rates were significantly greater in the control group compared to the esmolol-treated group at C and D ($P<0.001$). The mean ± S.E. of systolic pressures in the esmolol group were: 150.2 ± 7.8 mmHg at A, 149.4 ± 6.4 at B, 153.9 ± 7.6 at C, 157.5 ± 7.6 at D, and 119.6 ± 6.6 at E. In the control group, the corresponding systolic pressures were 140.7 ± 4.5, 141.7 ± 6.4, 188.8 ± 8.5, 179.7 ± 8.3 and 142.7 ± 8.8. The systolic blood pressure was significantly greater in the control group compared to the esmolol-treated group at C ($P<0.01$). Plasma free-NE levels were: 205.33 ± 33.04 pg/ml at A, 194.45 ± 45.1 at B, 379.83 ± 107.1 at C, and 290.0 ± 52.6 30 min. after esmolol, while in the control group, the corresponding blood levels were: 263.9 ± 48.9, 262.5 ± 52.8, 430.2 ± 108.56 and 324.8 ± 59.9 pg/ml. The post-intubation increases were not statistically significant in either group ($p>0.05$) despite a greater than 50% increase in mean values. Epinephrine and dopamine level changes were inconclusive.

Discussion. Patients pretreated with esmolol are protected from tachycardia caused by endotracheal intubation. Esmolol moderated the increases in systolic blood pressures. Esmolol infusion may offer an important pharmacological intervention in patients in whom an increase in heart rate, blood pressure and/or rate-pressure product should be avoided during endotracheal intubation.

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Title: RECOVERY AFTER OUTPATIENT ISOFLURANE AND ENFLURANE ANESTHESIA

Authors: K Korttila, M.D., and J Valanne, M.D.*
Affiliation: Unihammas Inc and Departments of Anaesthesia, Lappi Central Hospital*, Rovaniemi
and Helsinki University Central Hospital, Helsinki, SF-00290 Finland

Introduction. Rapidly increasing hospital expenses have produced a common trend towards outpatient anesthesia. We have previously tested recovery and residual effects of a number of drugs and anesthetic techniques.[1] The present study was conducted to compare recovery in patients undergoing dental or oral surgery under enflurane or isoflurane anesthesia. Furthermore, we wanted to evaluate the influence of the duration of the anesthesia on rapidity of recovery with both anesthetics.

Methods. One hundred and twenty patients were entered. The protocol was approved by institutional ethical committee and informed consent was obtained from each patient for the study. No premedication was used. Anesthesia was induced with methohexital and endotracheal intubation was facilitated with succinylcholine (1 mg/kg). Anesthesia was maintained with either enflurane or isoflurane in nitrous oxide and oxygen (50%) administered in a non-rebreathing circuit using spontaneous respiration. Enflurane (Efrane^{R}, Abbott) and isoflurane (Forane^{R}, Abbott) were used in random order and both the patient and the person administering the recovery tests were unaware which anesthetic had been used. No other drugs were given before or during anesthesia. The time elapsed until the patients were orientated to time and place after cessation of nitrous oxide administration was registered. The patients ability to walk on a straight line was recorded 30 and 60 min after anesthesia. The perceptual speed test was administered before and 30 and 60 minutes after anesthesia. The patients' task was to mark every digit in the row as the one circled at the beginning of the row for 2 minutes.[2] Student's t-test and chi-square test were used for statistical treatment of the results.

Results. Summary on findings is presented in Tables 1. and 2. The patients' ability to walk on a straight line normalized significantly ($P < 0.05$) faster after isoflurane than after enflurane anesthesia. Long enflurane anesthesia (over 90 min) was associated with significantly ($P < 0.05$) slower recovery than short enflurane anesthesia (less than 40 min), which was not the case with isoflurane. With isoflurane the rapidity of recovery did not depend on the duration of anesthesia. Most patients were discharged from the clinic one hour after anesthesia with a responsible adult.

Discussion. The tests used in this study were selected to help in making a clinical decision regarding discharge of patients from the clinic. Using a driving simulator we have previously shown that no major differences exists in the residual effects after brief halothane or enflurane anesthesia.[3] The faster recovery from isoflurane than from enflurane anesthesia in this study agrees with the modest solubility of isoflurane into blood. It is concluded that from the three inhaled anesthetics, halothane, enflurane and isoflurane, isoflurane should be preferred in outpatient practice due to rapid recovery after its administration.

Table 1. Characteristics of patients and summary of findings(mean ± SD) after outpatient general anesthesia with enflurane or isoflurane for oral surgery or dentistry. *$P < 0.05$ vs enflurane.

	Enflurane	isoflurane
Patients		
n	60	60
Age (yr)	28 ± 5.6	28 ± 5.4
Weight (kg)	71 ± 12	72 ± 13
Male/female	43/17	40/20
Methohexital (mg/kg)	1.93 ± 0.19	1.99 ± 0.10
Duration of Anesthesia (min)	66 ± 30	76 ± 34
Orientated to time and place (min)	13 ± 4	12 ± 4
Unsteady gait (% of total)		
after 30 min	77	75
after 60 min	25	10*
Perceptual speed (number correct)		
before anesthesia	51 ± 11	49 ± 8
after 30 min	42 ± 14	43 ± 12
after 60 min	59 ± 14	58 ± 13
Nausea or vomiting during 24 h (% of total)	25 %	26 %

Table 2. Influence of duration of anesthesia on rapidity of recovery.

	Enflurane		Isoflurane	
Assessment	< 40 min	> 90 min	< 40 min	> 90 min
Number of patients	13	14	9	17
Unsteady gait (% of total)				
after 30 min	62	100*	67	78
after 60 min	23	39	22	6
Perceptual speed number correct (mean ± SD)				
before anesthesia	50±11	49± 9	47±6	49±7
after 30 min	47±13	32±15**	45±13	38±11
after 60 min	62±48	38±13*	58±15	56±11

*$P < 0.05$, **$P < 0.01$ vs enflurane < 40 min

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Title: SPINAL CORD BLOOD FLOW FOLLOWING SUBARACHNOID LIDOCAINE

Authors: R Kozody, M.D., J Swartz, M.D., RJ Palahniuk, M.D., D Biehl, M.D., JG Wade, M.D.
Affiliation: Department of Anesthesia, University of Manitoba, Winnipeg, Manitoba
Canada R3E 0Z3

Introduction. This study was undertaken to determine the effects of subarachnoid lidocaine with and without epinephrine on spinal cord blood flow (SCBF) in dogs.

Methods. Eighteen mongrel dogs weighing 23 ± 4 kg (mean ± S.D.) were anesthetized with pentobarbital, intubated, and ventilated with an $F_iO_2 = 1.0$ to a $PaCO_2$ of 35-42 mmHg.

The radioactive microsphere technique was employed for spinal cord blood flow measurements[1]. Cerium^{141}, Chromium^{51}, or Strontium^{85} labelled 15 ± 0.5 micron microspheres were injected through a left ventricular catheter and sampled through a femoral arterial line.

Hemodynamic measurements were made through a femoral arterial line and a Swan-Ganz thermodilution catheter.

Following completion of the surgical preparation and stabilization of the $PaCO_2$, pH, temperature and blood pressure, a control SCBF was determined. A dural puncture was then performed at the L_5-L_6 or L_6-L_7 interspace.

Animals were divided into 3 equal groups. The dogs in each group received one of the following:

1. Preservative free 0.9% saline (N.S.) - 5 ml,
2. Lidocaine 100 mg in saline - 5 ml, or
3. Lidocaine 100 mg with epinephrine 200 ug in saline - 5 ml

Intravenous 0.9% saline solution was administered to maintain venous pressure at pre-injection values. Repeat determinations of SCBF were performed at 20 and 40 minutes following spinal anesthesia.

All data were analyzed using analysis of variance and Student's paired and unpaired t tests where appropriate.

Results. The results are summarized in the following table.

Saline (control group) n = 6	Pre Injection	20 min post injection	40 min post injection
MABP (mmHg)	127± 5	122±4	131± 4
C.I. (ml/kg/min)	233±19	198±8	206±13
Cervical Cord B.F. (ml/100g/min)	26± 3	26±5	20± 2
Thoracic Cord B.F. (ml/100g/min)	21± 3	22±3	19± 2
Lumbosacral Cord B.F. (ml/100g/min)	32± 5	39±9	35±10

Lidocaine (plain) n = 6	Pre Injection	20 min post injection	40 minpost injection
MABP (mmHg)	123± 2	93± 5*	106± 3*
CI (ml/kg/min)	230±32	204±35	203±36
Cervical Cord B.F. (ml/100g/min)	16± 2	13± 2	13± 1
Thoracic Cord B.F. (ml/100g/min)	13± 2	12± 2	13± 1
Lumbosacral Cord B.F. (ml/100g/min)	21± 2	35± 7	50± 9*

Lidocaine with Epinephrine n = 6	Pre injection	20 min post injection	40 min post injection
MABP (mmHg)	123± 4	76± 6*	82± 5*
C.I. (ml/kg/min)	186±20	240±18	228±32
Cervical Cord B.F. (ml/100g/min)	22± 4	20± 3	19± 2
Thoracic Cord B.F. (ml/100g/min)	17± 3	12± 1	13± 3
Lumbosacral Cord B.F. (ml/100g/min)	30± 4	24± 4	36± 9

Results are mean ± SEM, *p 0.05

Following subarachnoid lidocaine (plain, and with epinephrine) a significant decrease in MABP was evident at 20 and 40 minutes. Cardiac index however, remained unchanged during the study period in the 3 groups. Dural puncture and intrathecal N.S. did not significantly alter SCBF. Lumbar subarachnoid lidocaine did not alter cervical or thoracic SCBF. Lumbosacral SCBF was not significantly altered at 20 minutes following intrathecal lidocaine but increased 138% at 40 minutes. The addition of epinephrine to lidocaine prevented the increase in SCBF seen with lidocaine (plain) and flows remained similar to control values.

Summary and Conclusion. A significant increase in lumbosacral SCBF was demonstrated at 40 minutes but not at 20 minutes following intrathecal lidocaine. The hyperemic response seen with lidocaine at 40 minutes is similar to that occurring following subarachnoid tetracaine (20 mg) in dogs[2]. The addition of epinephrine (200 ug) to intrathecal lidocaine prevented the increase in SCBF seen at 40 min with lidocaine alone.

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TITLE: REDUCTION IN HALOTHANE MAC: COMPARISON OF MORPHINE AND ALFENTANIL

AUTHORS: C. L. Lake, M.D., C. A. DiFazio, M.D., Ph.D, J. C. Moscicki, M.S., and J. S. Engle, B.S.

AFFILIATION: Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, VA 22908

Introduction. While morphine has been observed clinically to produce essentially complete anesthesia, animal studies have documented a maximal enflurane MAC reduction of 65% by morphine (1). Sufentanil, a more potent narcotic produces nearly complete anesthesia, reducing halothane MAC by 90% (2). Alfentanil, a derivative of fentanyl, is shorter acting than fentanyl, but more potent than morphine. This study compares the reduction in halothane MAC produced by morphine and alfentanil in rats.

Methods. The anesthetic potency of alfentanil and morphine was measured by its reduction of the MAC of halothane. Fifty-two male Sprague-Dawley rats weighing 304±32 gms were anesthetized with halothane and oxygen at concentrations sufficient for endotracheal intubation and cannulation of the femoral artery and vein. The concentration of halothane was then reduced to 1% and ventilation controlled with a Harvard animal respirator. Body temperature and arterial blood gases were maintained within normal limits. The tail clamp technique was used to determine MAC. A PE10 catheter was introduced into the endotracheal tube until resistance was met, then withdrawn 1-2 mm. Alveolar concentrations of halothane were determined on gas samples drawn over a 3-5 minute interval into glass syringes at the time of tail clamp and assayed on a Hewlett-Packard Model 5750 gas chromatograph with a flame ionization detector. The halothane MAC reduction produced by morphine after doses of 4, 8, 12 or 20 mg/kg S.C. or intravenous infusion of alfentanil at .01 μg/kg/min to 100 μg/kg/min was determined using the tail clamp technique. Halothane was adjusted in decrements of 0.12% until a positive response was observed using 15 minute intervals for equilibration. A bolus dose of alfentanil equivalent to 10 minutes of infusion preceded the constant infusion.

Results. The control MAC for halothane was 0.78±0.12%, similar to previous observations in rats. The reduction of halothane MAC by morphine was biphasic with a rapid linear increase in MAC reduction up to 8 mg/kg and a slower rise from 8 to 20 mg/kg of morphine. At the highest dose used, the reduction of MAC by morphine was 87% (fig. 1). The maximal reduction in MAC produced by alfentanil that could be determined in this model was 35% at 15 μg/kg/min (table 1). Doses of alfentanil greater than 15 μg/kg/min produced severe truncal, chest wall, and abdominal rigidity in the animals, precluding adequate ventilation and determination of MAC.

Discussion. This study demonstrates that morphine, like sufentanil, can produce almost complete anesthesia. The difference between our results and those previously reported are probably caused by differences in anesthetic agents used and in the mode of drug administration. It would appear that opioids supplement halothane anesthesia better than they supplement cyclopropane or enflurane anesthesia and that almost complete anesthesia can be produced by morphine or sufentanil. In contrast, this study also demonstrates that alfentanil produces rigidity at doses that only produce a 35% MAC contribution. This implies that in contrast to morphine and sufentanil, the use of higher dose, alfentanil-supplemented anesthesia will require the use of a neuromuscular blocking drug.

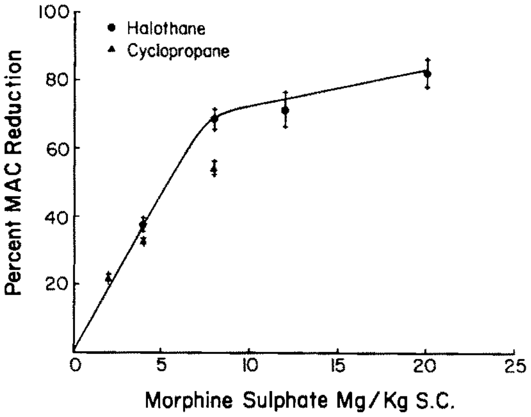

Figure 1. Reduction of halothane MAC by morphine. For comparison, previous data demonstrating reduction of cyclopropane MAC by morphine is included (3).

Table 1. MAC Reduction by Alfentanil

N	Alfentanil Dose (μg/kg/min)	MAC Reduction (% halothane)
4	0.01	0
2	0.1	2
2	1.0	11
5	5	16
7	10	26
2	15	35
14	20-100	Rigidity

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Title: **EFFECTS OF MILD HYPOTHERMIA ON BRAIN STEM AUDITORY AND SOMATOSENSORY EVOKED RESPONSES**

Authors: **AM Lam, M.D., J. Contreras, M.D., JF Keane, M.D., PH Manninen, M.D., and S Brown, M.D.**
Affiliation: **Department of Anaesthesia, University of Western Ontario, London, Canada. N6A 5A5**

Introduction.

Monitoring of sensory evoked responses can provide important information about nerve conduction through respective anatomical pathways. Of the non-pathological factors that may influence these electrophysiological potentials, body temperature is an important variable. While this may have minimal significance in awake patients as body temperature varies little, important deviation from normality may occur in anesthetized patients. In patients undergoing hypothermic cardiopulmonary bypass, brain stem auditory evoked responses (BAEP) were unrecordable below 25°C and progressive increase in peak V latency was observed before this end point (1,2). The patients studied, however, were all under the influence of various anesthetic agents. We sought to identify the influence of mild hypothermia (35°C) as occurred frequently intraoperatively on BAEP and somatosensory evoked responses (SSEP) in conscious human volunteers.

Methods.

Informed consents were obtained from six healthy male subjects, age 28-34. Mild hypothermia was induced by intravenous infusion of refrigerated Lactated Ringer's Solution and surface hypothermia with a cooling blanket. Temperature was monitored with a nasopharyngeal probe and maintained at the lowest level possible without invoking shivering. BAEP was recorded from the vertex in reference to ipsilateral ear lobe in response to monaural repetitive auditory clicks with alternating polarity at 21.1 Hz with bandpass filter between 150 to 1500 Hz. Disposable plastic ear inserts were used to deliver the auditory stimuli, causing a delay in all peaks by 0.5 msec. At least 1000 sweeps were averaged. SSEP was recorded from the contralateral sensory cortex, C_7 spine, and the Erb's point ipsilateral to the median nerve stimulated with a square wave 2 mA above twitch threshold. Either 128 or 256 responses were averaged. All sensory evoked responses were determined in duplicate during normothermia and hypothermia maintained for at least 10 minutes. Paired t-test was used for statistical analysis and $p<0.05$ was considered significant.

Results.

An average of 2500 ml Lactated Ringer's Solution was administered to each volunteer. The subjects tolerated mild hypothermia (35°C) well but started to shiver when the nasopharyngeal temperature decreased by more than 1.5°C. Changes in BAEP latencies and SSEP latency of the cortical response (N 20), spinal responses (N 13) and Erb's point response (N 10) as well as the central conduction time (CCT, difference between N 20 and N 13) are tabulated as shown. With the exception of peak IV-V, mild hypothermia to 35°C did not increase latency significantly. Interpeak latencies (IPL) were likewise unchanged. The increase in peak IV-V latency, although statistically significant, was only 0.05 msec. The amplitude decreased from 0.47 μV to 0.42 μV, but this difference was not statistically significant. In contrast, both latency and amplitude of N 10 and N 13 were significantly prolonged and decreased by hypothermia. The cortical component (N 20) was not significantly affected.

Discussion.

When interpreting intraoperative changes in sensory evoked responses, non pathological factors must be taken into account. Significant increase in BAEP latency can occur when temperature falls below 34°C. However, in most clinical conditions only mild hypothermia is encountered. Our study suggested that increase in peak IV-V latency is small at 35°C, and that analysis of IPL may be helpful because of the lack of change. In contrast, with SSEP, peripheral conduction is significantly prolonged by mild hypothermia while the cortical component is not significantly affected. CCT probably remains a valid derived variable for detection of changes. The delay in peripheral conduction in the present study, however, was quite possibly due to peripheral cooling much in excess of core cooling. We conclude that intraoperative BAEP and SSEP can be reliably recorded during mild hypothermia down to 35°C. Beyond this the effect of temperature must be taken into consideration in the interpretation of changes.

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BAEP

LATENCY (msec ± SEM)

TEMP	I	II	III	IV/V	I-III	I/V	III-V
36.2	2.35	3.47	4.52	6.40	2.17	4.05	1.88
±0.10	±0.06	±0.07	±0.45	±0.07	±0.04	±0.08	±0.04
35.0	2.35	3.45	4.56	6.45*	2.21	4.10	1.90
±0.10	±0.08	±0.10	±0.06	±0.08	±0.07	±0.10	±0.05

	LATENCY (msec ± SEM)				AMPLITUDE (μV ± SEM)		
TEMP	N10	N13	N20	CCT	N10	N13	N20
36.2	9.97	13.45	20.18	6.65	6.16	3.71	1.94
±0.10	±0.14	±0.26	±0.38	±0.42	±0.87	±0.29	±0.35
34.9	10.32*	13.82*	20.57	6.73	4.43*	3.03*	1.49
±0.12	±0.14	±0.22	±0.35	±0.36	±0.61	±0.28	±0.16

n = 6 *$p < 0.05$

Title: **EFFECTS OF HYPERTONIC SALINE ON EXTRAVASCULAR LUNG WATER OF SHEEP IN HEMORRHAGIC SHOCK**

Authors: A.J. Layon, M.D., D. Duncan, B.S., T.J. Gallagher, M.D., and M.J. Banner, R.R.T.

Affiliations: Departments of Anesthesiology and Surgery, University of Florida College of Medicine, Gainesville, Florida 32610

Introduction. We undertook this study to determine the effects on extravascular lung water (EVLW) of using a hypertonic crystalloid solution (3% saline) to treat hemorrhagic shock.

Materials and Methods. Seven sheep weighing between 43 and 75 kg were anesthetized with thiamylal sodium (loading dose: 15 mg/kg). After tracheal intubation, mechanical ventilation was maintained at 8 breaths/min with a tidal volume of 15 ml/kg. End-expiratory pressure was set at 0 cm H_2O (F_IO_2: 0.5) throughout the study. Pulmonary artery (PAP), pulmonary capillary wedge (PCWP), central venous (CVP), and mean arterial (MAP) pressures; cardiac output (CO) by thermodilution; and EVLW by the thermal-dye technique (1) were monitored. Colloid oncotic pressure (COP) (Wescor) and serum sodium, potassium, and osmolality were also measured. COP - PCWP gradient and venous admixture (Qsp/Qt) were calculated. After baseline measurements, the animals were bled via an arterial catheter to a MAP of 50 mmHg. Further bleeding was used as necessary to keep MAP at 50 mmHg. After 30 min at 50 mmHg, data were collected. Animals were then infused with hypertonic saline solution at approximately 500 ml/15 min. Therapeutic end point was baseline CO, MAP, and PCWP; fluid resuscitation was continued to maintain those values for 1 h. Final measurements were compared with those before shock and immediately after resuscitation. Analysis of variance and Duncan's test were used for statistical analyses.

Results (Tables 1 and 2). After fluid resuscitation, CO, PAP, and PCWP returned to baseline. MAP was still significantly lower than baseline 60 min after resuscitation. As expected, COP and COP-PCWP decreased significantly as volume was infused, but EVLW did not vary throughout the study. The volume of hypertonic solution needed to resuscitate each animal was 39 ± 19 ml/kg. Serum sodium, potassium, and osmolality varied significantly. Qsp/Qt increased from 1% to 4% by the end of the study.

Discussion. We investigated the effects on EVLW of treating hemorrhagic shock by rapidly infusing hypertonic saline. Even though the COP-PCWP decreased significantly, EVLW did not change. The known determinants of fluid flux across a capillary are hydrostatic and interstitial fluid pressure gradients, plasma and tissue oncotic pressures, a reflection coefficient, and lymph flow (2). Data indicate that, despite known changes in COP and COP-PCWP gradient, EVLW accumulation cannot be predicted; probably compensatory changes occur in the other unmeasured Starling factors. Also, the resuscitation fluid's hypertonicity may influence fluid movement in the direction of the intravascular compartment. Although unlikely, the time allotted for the study of these animals may not have been long enough to observe changes in EVLW. The marked increase in serum sodium and osmolality may be caused by either the solution's hypertonicity, its rapid infusion, or both. A recent study indicates that initially infusing hypertonic solution at 500 ml over 10–15 min and then more slowly, 500 ml/h, will yield less dramatic variation in serum sodium (3). Interestingly, the volume of 3% saline required for resuscitation (39 ± 19 ml/kg) was markedly less than the volume of lactated Ringer's solution (72.9 ± 81.9 ml/kg) that was required in a study using the same protocol (4). In conclusion, rapid infusion of hypertonic saline during hemorrhagic shock neither increased EVLW nor compromised gas exchange.

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Table 1. Effects of Hypertonic Solution on Shock*

	Before Shock	30 Min After Shock	Time After Resuscitation	
			Immediate	60 Min
PAP	19.4 ± 2.5	17.0 ± 5.9	20.0 ± 7.2	20.4 ± 6.0
PCWP	13.1 ± 4.9	10.0 ± 4.6†	13.6 ± 4.4‡	14.1 ± 4.8‡
MAP	127.1 ± 14.8	49.3 ± 8.4†	110.0 ± 10.8†	103.6 ± 16.8†
CO	5.05 ± 2.4	2.3 ± 0.8†	5.1 ± 1.5‡	6.3 ± 2.4‡
EVLW	11.6 ± 5.8	8.8 ± 4.1	8.0 ± 3.0	9.9 ± 4.6
COP	20.6 ± 1.5	16.8 ± 1.6†	12 ± 1.8†‡	11.5 ± 2.3†‡
COP-PCWP	7.4 ± 6.0	6.8 ± 5.2	-1.6 ± 5.7†‡	-2.6 ± 6.2†‡
Qsp/Qt	0.9 ± 0.6	1.1 ± 1.1	2.1 ± 2.4	4.1 ± 4.5†‡

*Values are means ± SD. Abbreviations are defined within the text. Units of measure: all pressures, mmHg; CO, L/min; EVLW, ml/kg; and Qsp/Qt, %.

†$P < 0.05$ compared with before shock.

‡$P < 0.05$ compared with 30 min after shock.

Table 2. Effect of Hypertonic Fluid on Serum Values After Shock*

	Before Shock	Time After Resuscitation	
		Immediate	60 Min
Na+ (mEq/L)	150.8 ± 2.3	167.8 ± 9.2†	183.3 ± 15.4†
K+ (mEq/L)	3.2 ± 0.3	2.3 ± 0.4†	2.6 ± 0.7†
Osm (mOsm/kg H_2O)	298.3 ± 1.4	330.8 ± 10.7‡	352.3 ± 21.4†
Resuscitation volume (ml/kg)	-	-	39.0 ± 19

*Values are means ± SD.

†$P < 0.05$ compared with before shock.

‡$P < 0.05$ compared with 60 min after resuscitation.

Title: TRACHEAL GAS LEAK AND INTRAOPERATIVE TRACHEAL ASPIRATION IN CHILDREN

Authors: KW Terry Lee, M.D., RM Dougal, CRNA, JJ Templeton, M.D., and JJ Downes, M.D.

Affiliation: Department of Anesthesia and Critical Care, The Children's Hospital of Philadelphia, and the University of Pennsylvania, Philadelphia, Pennsylvania

Introduction. The incidence of aspiration in children mechanically ventilated via uncuffed endotracheal tubes has been reported to be as high as 77%(1). However, the relationship between endotracheal tube (ETT) fitness (i.e. loose vs. tight) and aspiration during controlled ventilation in children is not known. This study therefore was undertaken in children to determine the following: 1) the incidence of aspiration and its relationship to ETT fitness at peak inflating pressure (PIP)during controlled ventilation with uncuffed ETTs and 2) the clinical significance of the ensuing aspirations.

Methods. We studied 184 patients retrospectively and 236 patients prospectively to determine the incidence of tracheal aspirations of gastric secretions and blood during endotracheal anesthesia with neuromuscular blockade and controlled ventilation. Age ranged from newborn to 10 years. Tube size was selected on the basis of previously reported criteria (2). Uncuffed Murphy PVC tracheal tubes from the same manufacturer were inserted by direct laryngoscopy performed with neuromuscular blockade. Following intubation, laryngotracheal fitness of the tube was defined in each patient as the PIP in cms H_2O at which a leak was audible over the larynx, and the stomach was suctioned with a 14 Fr. suction catheter. The patients were managed with controlled ventilation for 0.5 to 4 hours until extubation. None of the children had evidence of aspiration at laryngoscopy. We reviewed the records of patients undergoing non-oral operations (Group 1:N=184) who had a gas leak of 5-20 cmH_2O to determine if signs of pneumonia occurred. Patients undergoing oral operations (Group 2:N=136) and non-oral operations (Group 3:N=100) were selected for prospective study. Group 2 was further divided into 2 subgroups with a gas leak at 5 to 10 cmH_2O (Group 2A:N=68) and 10 to 20 cmH_2O (Group 2B:N=68). Patients in Group 3 (N=100) underwent procedures involving body surface and extremities with a gas leak at 5 to 20 cmH_2O. Following extubation, occurrence of intraoperative aspiration was defined postoperatively as follows: Group 1- clinical evidence of pneumonitis; Group 2- presence of blood (determined by Hematest tablet) at the distal tip of the ETT; Groups 2 and 3- presence of acidic ($pH \leq 2.5$ by litmus paper) secretions at the distal tip of the ETT; this was considered indicative of the presence of gastric fluid. Informed consent was obtained from parents and approval was granted by the Committee for the Protection of Human Subjects.

Results. None of the patients in Groups 1 or 3 had evidence of aspiration. The Group 2A children (Table 1) with looser fitting tubes had an incidence of 48% of blood aspiration. This was significantly lower than the Group 2B patients with tighter fitting tubes who had an overall incidence of blood aspiration of 69% (X^2 5.13; corrected $p<0.05$). In spite of this difference, none of the children in either group needed the usual tracheal suctioning measures. None of the patients in Groups 2 and 3 had a tracheal tube secretion $pH \leq 3.0$ (Table 2); only 2/236 had pH of 4 and the remaining 95% had a pH 6 or 7.

Discussion. The results indicate that clinically significant aspiration does not occur during elective endotracheal anesthesia with controlled ventilation in infants and children. However, controlled ventilation when applied via looser fitting tubes does decrease the incidence of blood aspiration during general anesthesia for intraoral surgical procedures. We speculate that this occurs because of the delivery of fresh gas flow at high velocities during controlled ventilation. Due to the resulting vortex dynamics at the tip of the ETT some of the fresh gas exits cephalad around the ETT towards the oropharynx and thereby preventing the cauded movement of blood and secretions into the larynx and trachea.

In conclusion, the incidence of blood aspiration is lower in children undergoing intraoral surgical procedures during controlled ventilation via an ETT and with an audible leak at 5-10 cmH_2O than those with an audible leak at 10-20 cmH_2O. The aspiration of acid gastric fluid ($pH \leq 2.5$) during elective endotracheal anesthesia with controlled ventilation was not seen in our patient population.

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Table 1. INTRALUMINAL TRACHEAL TUBE BLOOD OCCURRING IN INTRAORAL PROCEDURES

PROCEDURES	N	LEAK PRESSURE (cmH_2O)	GROSS BLOOD	OCCULT BLOOD ONLY	TOTAL BLOOD
T & A	54	5-10	6	15	21
	54	10-20	6	27	33
PHARYNGEAL	3	5-10	0	2	2
FLAP	3	10-20	3	0	3
CLEFT	7	5-10	2	5	7
PALATE	7	10-20	3	4	7
DENTAL	4	5-10	1	2	3
PROCEDURES	4	10-20	2	2	4
ALL	68	5-10	9(13%)	24(35%)	33(48%)
PROCEDURES	68	10-20	14(21%)	33(49%)	47(69%)

Table 2. INTRALUMINAL TRACHEAL TUBE pH OCCURRING IN INTRAORAL AND SUPERFICIAL PROCEDURES

PROCEDURES	N	LEAK PRESSURE (cmH_2O)	pH 3	4	5	6	7
T & A	54	5-10	0	0	5	9	40
	54	10-20	0	0	2	2	50
PHARYNGEAL	3	5-10	0	0	0	0	3
FLAP	3	10-20	0	0	0	0	3
CLEFT	7	5-10	0	0	0	1	6
PALATE	7	10-20	0	1	0	0	6
DENTAL	4	5-10	0	0	0	0	4
PROCEDURES	4	10-20	0	0	1	0	3
SUPERFICIAL PROCEDURES	100	5-20	0	1	1	52	46
ALL			0	2	9	64	161
PROCEDURES	236			(0.8%)	(3.8%)	(27%)	(68%)

Title: EFFECTS OF INTRAVENOUS LIDOCAINE AND HIGH-DOSE PANCURONIUM ON INTRAOCULAR PRESSURE IN CHILDREN

Authors: J Lerman, M.D., F.R.C.P.(C), AA Kiskis, M.D.*

Affiliation: Departments of Anaesthesia and Ophthalmology*, The Hospital for Sick Children,
University of Toronto, Toronto, Ontario, Canada

Introduction. High-dose pancuronium (0.15 mg/kg) provides rapid muscle relaxation in patients with open eye injuries and full stomachs. Although high-dose pancuronium does not significantly increase intraocular pressure itself(1), the effectiveness of high-dose pancuronium, followed by thiopentone, and atropine in attenuating the intraocular response to laryngoscopy has not been established. Intravenous lidocaine has been effective in attenuating the reflex circulatory responses to laryngoscopy(2) and may further attenuate the reflex intraocular responses to laryngoscopy. Therefore, we determined the effectiveness of this drug regimen with and without intravenous lidocaine to attenuate the intraocular pressure response to laryngoscopy and endotracheal intubation.

Methods. With approval from the committee on human research and informed written consent, 20 patients, ages 1-10 years, scheduled for minor surgery and requiring endotracheal intubation, were studied. The patients were ASA 1 or 2, fasting, and unpremedicated. Patients were excluded if there was any history of glaucoma or intraocular disease, renal insufficiency, neuromuscular disease, or if a difficult intubation was anticipated. After inserting a #25 gauge butterfly in the hand, either sterile water (2 ml) (n=10) or preservative-free lidocaine (1.5 mg/kg) (n=10) was administered, followed immmediately by pancuronium 0.15 mg/kg. As soon as evidence of weakness appeared, anesthesia was induced with a mixture of thiopentone (5 mg/kg) and atropine (0.02 mg/kg). 100% oxygen was administered for one minute. After a rapid atraumatic oral intubation, ventilation was controlled with 1-1.5% halothane in a nitrous oxide/oxygen (70/30) mixture to maintain normocapnia. Intraocular pressure was measured with a hand-held Perkins applanation tonometer, at the time of loss of the eyelid reflex (control time 0), immediately after intubation, and each minute thereafter for five minutes. Heart rate and blood pressure were also recorded. Positive end-expiratory pressure was avoided. External pressure on the eye was avoided. All patients were horizontal and supine throughout the study period. Statistical significance ($P < 0.05$) was determined using the Bonferonni t test, two-way ANOVA, and the Student-Newman-Keuls multiple range test.

Results. Age, weight, and control values for intraocular pressure, heart rate and blood pressure did not differ between the two groups. In the group pretreated with sterile water, intraocular pressure increased significantly ($P < 0.05$) above control values after laryngoscopy whereas in the group pretreated with lidocaine, intraocular pressure did not increase after laryngoscopy, but decreased significantly below control values within 5 minutes ($P < 0.05$) (figure). In the group pretreated with sterile water, intraocular pressure was significantly greater than in the group pretreated with lidocaine at all times ($P < 0.05$), except for control values (figure). Heart rate and systolic blood pressure were unchanged during the study period.

Discussion. Intraocular pressure increased significantly ($P < 0.05$) after laryngoscopy and endotracheal intubation in children anesthetized with high-dose pancuronium followed by thiopentone and atropine, although the increase was less than reported previously with other drug regimens(1). Pretreatment with intravenous lidocaine (1.5 mg/kg) immediately prior to pancuronium, significantly attenuated the increase in intraocular pressure after laryngoscopy and endotracheal intubation. The latter drug regimen is recommended for induction of anesthesia in children with open eye injuries and full stomachs, providing there are no contra-indications to the regimen (see methods) and a secure intravenous access is maintained.

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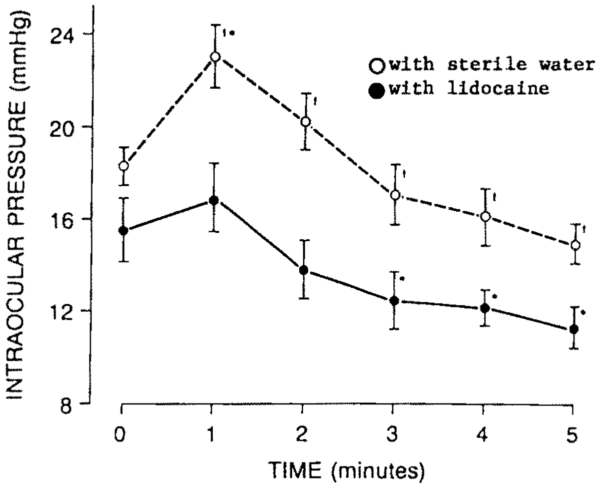
Figure



Data are Mean ± S.E.
* differ from control, $P < 0.05$
† differs from the lidocaine group, $P < 0.05$

Title: FLOW VERSUS VOLUME POSTOPERATIVE BREATHING DEVICES

Authors: JL Lichtor, M.D., AG Little, M.D.[*], H MacMahon, M.D.[*], and JV Courtney, M.D.[†]

Affiliation: Departments of Anesthesiology, Surgery[*], and Radiology[†], The University of Chicago
Medical Center, Pritzker School of Medicine, Chicago, Illinois 60637

Introduction. Some controversy exists as to the usefulness of postoperative breathing devices. These devices can either encourage a large inhaled volume or a rapid inspiratory flow. This study was designed to compare the effectiveness of these devices in preventing atelectasis in patients undergoing thoracic surgery.

Methods. Patients scheduled for thoracic surgery were visited on the day prior to operation by a physical therapist. They were randomly assigned to use postoperatively either Triflo (Cheeseborough Ponds, Inc.), a rapid inspiratory flow device or Volurex (DHD Medical Products), a large inhaled volume device. They were instructed in the use of the device and were again seen daily postoperatively by the physical therapist to ensure correct use of the device. In addition, they were postoperatively routinely encouraged by the nurses to use their device.

Chest radiographs obtained daily for the first six days postoperatively were reviewed by a radiologist. Each lung was divided into three zones, (upper, mid, and lower), and was graded for atelectasis on a scale of 1-5; a total score was then obtained by summating the scores for each zone. After discharge from hospital, patient age, sex, preoperative pulmonary functions, type of operation (resection of lung tissue, esophageal surgery, or thoracotomy) and daily highest temperature for five days postoperatively were recorded.

Patients were later excluded from the study if they required ventilation for more than twelve hours during the first week postoperatively, or if they died in the hospital prior to discharge.

Statistical analysis was performed using two-way analysis of variance (the effect of breathing device and postoperative day on temperature and X-ray score), chi-square (sex and type of operation for each device), and Student's T (age and preoperative pulmonary functions for each device) (1).

Results. A total of 60 patients were included in the study. The number of patients, male:female ratio, proportion undergoing each type of surgery, and preoperative pulmonary functions for each breathing device are listed in Table 1. No significant difference was found in the characteristics of either group. The overall highest temperature and radiologic atelectasis score are listed in Table 2.

Discussion. A variety of postoperative maneuvers are utilized to decrease postoperative pulmonary insufficiency. Bartlett (2) described an incentive spirometer based on the volume principle that diminished A-a gradient and reversed atelectasis. Many deep breathing devices currently used encourage only a rapid inspiratory flow rate. However, a rapid inspiratory flow could be achieved without obtaining a large tidal volume. The rapid flow devices are more popular because of cost as well as portability. Lederer (3) compared flow and volume devices and could find no difference in pulmonary functions or temperature on a daily basis. The use of these devices were left to the initiative of the patient. Also, they did not examine the overall effect of their devices on the measured variables.

In our study, patients using the Triflo had significantly less atelectasis and lower temperatures than patients using the Volurex. The radiographic appearance of atelectasis is nonspecific and the scores may represent other forms of pulmonary infiltrate. Yet, our findings are contrary to the feeling by many that the volume devices are preferable. Further work will be necessary to determine which breathing pattern is most effective in reducing postoperative atelectasis.

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Table 1

	Triflo	Volurex
Number of patients	33	28
M:F ratio	19/14	10/18
Lung resection/ esophageal/thoracotomy	15/12/6	9/9/10
FEV1-preop L/min	2.41	2.22
FVC-preop L/min	3.24	3.04
FEVL/FVC-preop	0.75	0.75

Table 2

	Triflo	Volurex	Significance
Temperature (°C)	37.5	37.8	$p<0.001$
Atelectasis Score	3.1	5.2	$p<0.001$

Title: ACCURACY OF RADIAL ARTERY PRESSURE MONITORING

Authors: CY Lin, M.D., B Beker, M.D., and E LaFontaine, M.D.[*]

Affiliation: Departments of Anesthesiology and Surgery[*], The University of Chicago Medical Center,
Pritzker School of Medicine, Chicago, Illinois 60637

Introduction. The change of cardiovascular status may occur rapidly, on a beat-to-beat basis in the critically ill patient, therefore, it is advantageous to rely on the direct intravascular blood pressure measurement in management of critically ill patients. Although change of intravascular pressure alone without a knowledge of the simultaneous change of blood flow, it is difficult to make full interpretation of hemodynamic changes, but clinically intravascular pressure monitoring still provide very important information about the changing status of the circulation. The radial artery (RA) is the most commonly cannulated site for direct arterial pressure monitoring during major surgery. Discrepancies have often been encountered between the pressure recorded from the RA and a central arterial pressure measured at the aortic root following cardiopulmonary bypass. Therefore, a prospective study was carried out comparing the arterial pressure obtained from the RA and the femoral artery (FA).

Methods. Thirty consecutive cases undergoing cardiac surgery with cardiopulmonary bypass were selected for the study. RA and FA were cannulated percutaneously with a #20 angiocath and connected to the same transducer with the same length of extension tubing. Pressures were recorded and compared at the following times: (1) control (prior to chest incision) (2) application of the sternal retractor, (3) during bypass, and (4) off bypass but prior to protamine administration. In the following table, the per cent variation of the RA pressure from the FA pressure is shown for the various times.

Results.	(1)	(2)	(3)	(4)
SYSTOLIC	98.4±5.1	91.8±11.1[@]		83.9±10.2[@]
range	(85-105)	(70-111)		(56-102)
DIASTOLIC	99.7±2.2	98.5±6.0		97.2±3.9[@]
range	(94-104)	(73-104)		(88-103)
MEAN	99.2±2.5	95.4±5.6[*]	93.2±9.4[*]	95.4±4.8[*]
range	(93-104)	(89-103)	(67-116)	(78-100)

@ P<0.005 * P<0.001

Discussion. The results demonstrate the inaccuracy of RA measurement following cardiopulmonary bypass. There is heavy reliance on hemodynamic measurements in the use of vasopressors in perioperative care. The underestimation of pressure by RA monitoring will be misleading and cause the inappropriate overusage of vasopressors in some clinical situations. Conversely, postoperative hypertension in the recovery room may be underestimated by the RA pressure reading and result in the perpetuation of excessive left ventricular overwork. A change in the peripheral vascular bed resistance, third space fluid shifts during bypass, and the application of the sternal retractor (similar to the thoracic outlet syndrome) may all contribute to the discrepancy. The comparison of RA pressure measurement and pressures obtained from an aortic root cannula immediately following bypass will demonstrate the degree of difference and protect the patient from possible mismanagement. Therefore, the central arterial pressure monitoring via femoral artery or brachial artery in lieu of radial artery should be recommended for the infants, and for the patients with poor left ventricular function.

Title: POTENTIATION OF VERAPAMIL-INDUCED CARDIOVASCULAR DEPRESSION BY PROPRANOLOL IN ANESTHETIZED DOGS

Authors: AA Lina, M.D., RS Rhodes, M.D., PJ Dauchot, M.D., S Derrer, M.D., and SA Lalka, M.D.
Affiliation: Departments of Anesthesiology and Surgery, University Hospitals and Case Western Reserve University, Cleveland, Ohio

Introduction. The beta blocker propranolol and the calcium entry blocker verapamil are often used for the treatment of tachydysrhythmias. Both propranolol (P) and verapamil (V) depress cardiac function. Reports on the interaction of P with V are controversial. In unanesthetized man on chronic P therapy, treatment with V has been reported on the one hand to have negligible (1) and on the other to have significant (2) negative inotropic effects. We investigated whether acute pretreatment with P alters the hemodynamic response to intravenous verapamil in anesthetized dogs.

Methods. Ten mongrel dogs (20 to 23 kg body-weight) were studied. Anesthetic management consisted of secobarbital (25 mg/kg I.V.), followed by tracheal intubation and maintenance of anesthesia with 50% N_2O in O_2 and isoflurane (1% inspired concentration). Mechanical ventilation of the lungs was adjusted to keep $PaCO_2$ between 35 and 40 mm Hg. Heart rate (HR) was obtained from the EKG. Retrograde catheterization of femoral and carotid arteries with 7 F Millar catheters provided left ventricular end-diastolic pressure (LVEDP), peak dP/dt and systemic blood pressure (BP). A 7F pulmonary artery (PA) catheter provided PA pressure (PAP) and PA occluded pressure (PAOP). Cardiac output (CO) was measured in triplicate by thermodilution (Edwards). Mean BP ($\overline{BP}$), mean PAP ($\overline{PAP}$), stroke volume (SV), systemic (SVR) and pulmonary (PVR) vascular resistance were derived from standard formulae. All dogs underwent laparatomy with exposure of the infrarenal abdominal aorta (IAA). A Gould-Statham electromagnetic flow probe was positioned around the IAA to measure IAA flow (QIAA). Five dogs (Group V) received an IV bolus of 300 mcgr/kg of verapamil over 2 min followed by a 20 min infusion of 6 mcgr/kg/min of V. Five other dogs (Group PV) received an IV bolus of propranolol (0.5 mg/kg), followed 20 min later by the verapamil regimen given to the dogs in Group V. Hemodynamic measurements were taken before the V bolus (baseline = B), 3 min following the completion of the V bolus injection (V_5) and after 20 minutes of V infusion (V_{20}). Analog signals were recorded on a 6-channel Gould strip chart recorder. Data analysis included one-way analysis of variance, Newman-Keuls tests and unpaired T tests.

Results. Mean values and standard deviations (SD) of hemodynamic variables appear in Table. At B, there were no statistically significant differences between the groups. Verapamil treatment caused in Group V overall statistically significant changes (one-way analysis of variance) in HR ($P < 0.05$), $\overline{BP}$ ($P < 0.005$), $\overline{PAP}$ ($P < 0.05$) and QIAA ($P < 0.01$). More specifically $\overline{BP}$ dropped and $\overline{PAP}$ and QIAA increased at V_5. At V_{20}, HR and $\overline{BP}$ were lower and $\overline{PAP}$, PVR and QIAA higher that at B. In Group PV, verapamil treatment resulted in overall significant changes (one-way analysis of variance) in HR ($P < 0.01$), $\overline{BP}$ ($P < 0.01$), CVP ($P < 0.01$) and peak dP/dt ($P < 0.005$). More specifically, HR, $\overline{BP}$, and peak dP/dt dropped at V_5. At V_{20}, HR, $\overline{BP}$ and dP/dt were still decreased and CVP increased as compared to B. The HR difference between B and V_{20} was significantly larger ($P < 0.025$) in the PV group (-19 beats/min) as compared to the V group (-7 beats/min).

Discussion. Verapamil depressed cardiovascular function in the presence as well as in the absence of propranolol. However, while HR and $\overline{BP}$ decreased in both groups, HR was much more affected in group PV. Further, P pretreatment seems to influence less the $\overline{PAP}$ and PVR response to V. Taking peak dP/dt as a more specific index of contractility, the cardiac depressant effect of V became much more apparent in the presence of P. Finally, P pretreatment appears to abolish verapamil-induced redistribution of blood flow to the IAA. In conclusion, in isoflurane-anesthetized dogs, pretreatment with propranolol enhances verapamil-induced negative cardiac chronotropic and inotropic effects.

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TABLE

	Group V (n = 5)			Group PV (n = 5)		
	B	V_5	V_{20}	B	V_5	V_{20}
HR(b/min)	124(9)	124(12)	117(15) * #	123(11)	111(17) *	104(14) **
$\overline{BP}$(mmHg)	125(27)	92(19) **	110(30) #	111(19)	89(15) **	92(10) **
$\overline{CVP}$(mmHg)	5(3)	3(2)	4(2)	4.2(1)	6.5(1) *	7.3(2) **
$\overline{PAP}$(mmHg)	11(3)	13(3) *	14(3) **	13(1)	14(2)	14(1)
PAOP(mmHg)	7.3(3)	7.6(2)	7.4(2)	11(4)	13(5)	13(5)
dP/dt(mmHg/s)	1499(223)	1220(454)	1327(542)	1395(346)	971(140) **	1008(135) **
LVEDP(mmHg)	8(4)	7(3)	9(4)	10(4)	12(3)	12(3)
CO(L/min)	3.5(.4)	3.7(.7)	3.1(.8)	3.1(1)	2.7(.9)	2.1(.6)
SV(cc/beat)	29(3)	29(4)	27(6)	25(8)	24(6)	21(5)
SVR(Units)	33(6)	26(3)	35(13)	37(14)	35(8)	42(11)
PVR(Units)	1.2(.5)	1.5(.7)	2.3(.5) *	1.2(1)	1.5(1.1)	1.8(1)
QIAA(cc/beat)	1.2(.4)	1.7(.5) **	1.5(.5) **	.9(.4)	1.0(.4)	.8(.3)

Mean values (SD) of hemodynamic variables before (B), 3 mins. after V bolus(V_5), and after 20 mins. of V infusion (V_{20}) with (Group PV) and without (Group V) propranolol pretreatment. Change from baseline($p < 0.05$ (*); $p < 0.01$ (**)) and change from previous condition($p < 0.05$ (#)) by Newman-Keuls test.

Title: **INTRACRANIAL PRESSURE AFTER ATRACURIUM IN CATS.**

Authors: B. Litwak, M.D., J. P. Giffin, M.D., J.E. Cottrell, M.D., C. Capuano, B.S., and C. Stein, M.D.

Affiliation: Department of Anesthesiology, State University of New York, Downstate Medical Center, and Kings County Hospital Center, Brooklyn, New York 11203.

Introduction. Muscle relaxants are selected for their safe use during neuroanesthesia based upon their hemodynamic and intracranial effects. Pancuronium is commonly used, and while it does not change intracranial pressure (ICP)(1), it does have significant cardiovascular effects(2). Succihylcholine and d-tubocurarine have been shown to have adverse effects on both parameters(3,4). Because atracurium, a new intermediate acting competitive neuromuscular blocking agent, has minimal cardiovascular effect(5), it may not have a significant effect on ICP, similar to vecuronium(6)., Heart rate (HR), ICP and mean arterial pressure (MAP) after atracurium were studied in cats with normal and artificially elevated ICP.

Methods. Six cats (4.0-5.0 kg) were anesthetized with intraperitoneal pentobarbital (33 ± 1 mg/kg); acepromazine (0.4 ± 0.1 mg/kg), intubated and ventilated with nitrous oxide 65% in oxygen to maintain a $PaCO_2$ of 34 ± 2 mmHg. Heart rate, MAP and arterial blood gas samples were obtained from a femoral artery catheter. Sciatic nerve twitch responses were recorded with a Grass force-displacement transducer. Rectal temperature was maintained at 36 ± 0.3°C throughout the experiment. A 19 gauge needle was secured in the cisterna magna (CM) to monitor ICP. Heart rate, ICP, MAP and twitch response were continuously recorded. With ICP normal, baselines were established and control measurements taken. Atracurium (0.4 mg/kg, 2xED 95) was injected and responses in MAP, HR, ICP were recorded until the twitch response returned to control.

Baselines were reestablished and ICP was increased by infusion of buffered Ringer's lactate solution throughout the CM needle to maintain ICP at 27 ± 1 mmHg. Control measurements were taken and drug administration was repeated for each group and responses recorded. Values for ICP, MAP and HR used for analysis were those of greatest change until time of recovery of twitch responses. Results were analyzed using the 2-tail paired "t" test.

Results. No significant change in ICP, MAP or HR could be detected after atracurium 0.4 mg/kg when ICP was normal or elevated (table). No apparent change in cerebral perfusion pressure (CPP) occurred during muscle paralysis with atracurium in normal or elevated ICP.

Conclusion. Atracurium, like vecuronium, a new intermediate acting muscle relaxant may be safe for use in neurosurgical patients with mass lesions since in this animal model at doses of 0.4 mg/kg, ICP, MAP, HR and CPP were not altered.

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Table: The effect of atracurium on ICP, MAP, HR and CPP in cats with normal and elevated ICP.

INITIAL ICP NORMAL

	Control	After Drug	Change
ICP*	4.7 ± 0.6	4.9 ± 0.8	0.25 ± 0.3
MAP*	87 ± 4	91 ± 5	4.2 ± 3
HR**	178 ± 5	182 ± 5	3.3 ± 6
CPP*	75 ± 6	76 ± 6	4.1 ± 3

ICP ELEVATED

	Control	After Drug	Change
ICP*	27.6 ± 1.3	26.6 ± 1.2	-1.0 ± 0.3
MAP*	102 ± 6	105 ± 5	2.4 ± 3.2
HR**	179 ± 6	183 ± 8	4.3 ± 3.1
CPP*	75 ± 6	76 ± 6	1.7 ± 1.7

* mmHg
** beats/minute

All values are mean ± standard error. n = 6, no changes were statistically significant.

Title: HALOTHANE HEPATOTOXICITY (HH) IN A GUINEA PIG (G-P) MODEL IN THE ABSENCE OF CONDITIONING FACTORS.

Authors: CA Lunam, B.Sc(Hons).,† MJ Cousins, M.D., F.F.A.R.A.C.S., * P de la M Hall, M.B.B.S., F.R.C.P.A. †
Affiliation: Depts. of Anaesthesia & Intensive Care * and Pathology.† Flinders Medical Centre, Flinders University of South Australia, S.A. 5042. Australia.

Introduction. Rat models of HH have required administration of halothane (H) with enzyme induction and hypoxia, or other "conditioning" factors. This paper reports a G-P model which does not require such factors.

Methods. **I. Time Course of HH.** 45 male outbred G-P were exposed to 1% H in air for 4h in a chamber which permitted control of temperature and respired gas concentrations. Groups of G-P were sacrificed on days 1, (n=10) 2, (n=15), 3 (n=10) and 7, (n=10) after H and serum alanine aminotransferase (ALT) measured. At each killing time unexposed G-P were killed. Liver sections were coded and examined by light microscopy (LM): *severe damage* was characterised by confluent necrosis around the central vein, *mild damage* by scattered foci of necrosis. **II. H. Metabolism and Hepatotoxicity of H.** 10 G-P were anesthetised(see experiment I) and 10 control G-P were placed in a similar chamber but breathed only room air for 4h. Breath samples were taken every 20min and assayed by GLC for 2-chloro-1,1-difluoroethylene (CDF) and 2-chloro-1,1,1-trifluoroethane (CTF). Urine was collected for 24h before and after H for measurement of trifluoroacetic acid (TFA) by NMR spectrometry, and for inorganic fluoride activity (F^-) by an ion specific electrode. 48h after H, all G-P were killed and serum ALT measured and liver pathology assessed. **III. Effect of SKF-525A.** 55 G-P were randomly divided into 4 groups: *Gp 1*, H 1% for 4h in air (n=20), *Gp 2*, SKF-525A 125mg/kg i.p., followed 1h later by H 1% for 4h in air (n=20); *Gp 3*, SKF-525A, 125mg/kg, i.p.(n=10) ; *Gp 4*, 0.9% NaCl 1ml/kg, i.p. (n=5). *Gp 1* and 2 G-P were anesthetised as in I and CDF, CTF determined. *Gp 3 and 4* G-P breathed air as in II. 48h later, all G-P were killed. Blood was collected for ALT and liver tissue for LM. **IV. Hemodynamics and Hepatotoxicity of H compared to isoflurane.** Cannulation of the left carotid artery was performed in 15 G-P after fentanyl 200 μ g/kg and 31mg/kg methohexital. G-P were allowed to recover and then received either 1% H (n=10) or 1.1% isoflurane (n=6) for 4h in air. Arterial blood gases were measured before, and at 1h intervals during, anesthesia. Mean arterial blood pressure (MAP) was continuously recorded (Mingograph 82). All G-P were killed at 48h for ALT and LM.

Results. I. 24h after H there was no evidence of HH. On day 2, 9 of the 15 G-P sacrificed had HH. Of these, 5 had severe liver necrosis and high ALT, 578.8 ± 121.2 (SEM) IU/l. The remainder had mild damage by LM and mild increases in ALT, 127.6 ± 11.1 (SEM) IU/l. The frequency and severity of damage was similar on day 3. On day 7 after H, HH was not apparent. 10 control G-P, had normal livers by LM, and by ALT 67.4 ± 6.9 (SEM) IU/l. **II.** Plateau levels of CTF, CDF were reached 80min after starting H: CTF, 2.5 ppm and CDF, 0.3 ppm. Urinary F^- was increased post H to 2.8 ± 0.3 (SEM) compared to pre-H, 0.8 ± 0.1 (SEM) μ mol/day ($P < 0.001$, Student's paired t test). Urinary TFA was undetectable pre-H and was 41 ± 5 (SEM) μ mol/day post-anesthesia. **III.** Administration of SKF 525A prior to H decreased levels of CTF, 1.3 ± 0.2 (SEM) ppm and CDF was undetectable compared to H treatment alone: CTF, 2.6 ± 0.1 (SEM) and CDF 0.5 ± 0.1 (SEM) ppm ($p < 0.001$, Student's unpaired t test). SKF 525A also decreased HH from 10/20 G-P in *Gp 1* to 4/20 G-P in *Gp 2* ($p <0.05$). 6/10 G-P with HH in *Gp 1* had severe damage whereas 4/4 with HH in *Gp 2* had only mild damage. **IV.** Pre-anesthesia MAP was 88 ± 4 (SEM) mmHg in *Gp 1* and 88 ± 5 (SEM) mmHg in *Gp 2*. The greatest decrease in MAP (Δ MAP) occurred within the first h of H 45 ± 2 (SEM) and during the second h of isoflurane 46 ± 3 (SEM). 4 G-P which developed severe HH following H had comparable Δ MAP 45 ± 3 (SEM) to those without HH, Δ MAP, 45 ± 4 (SEM). Liver damage was not observed in G-P administered isoflurane although they had similar Δ MAP. Blood gases during H and isoflurane were similar: e.g. for H anesthesia pO_2 83 ± 3 (SEM) mmHg, pCO_2 32 ± 2 (SEM) mmHg pH 7.4 ± 0.1.

Discussion. In G-P HH is associated with H metabolism without conditioning factors. HH is delayed in onset and occurs reproducibly, but only in a percentage of animals. Neither anesthesia *per se* nor alteration in cardiorespiratory function appear to be responsible for HH. Further studies in our laboratory have confirmed a similar response to H exposure in susceptible G-P one month after recovery, whereas non-susceptible G-P did not develop HH following re-exposure to H. The present data, and reports of a genetic influence on susceptibility to HH among different rat strains[1] and in some humans[2], indicate that pharmacogenetics is an important etiologic factor in HH. Also the G-P model provides the opportunity to study the pathogenesis of HH in the absence of conditioning factors[3].

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Title: **THE EFFECT OF ISOFLURANE INDUCED HYPOTENSION ON THE MYOCARDIUM**

Authors: PH Manninen, M.D., AM Lam, M.D., and AW Gelb, M.B.

Affiliation: Department of Anaesthesia, University of Western Ontario, London, Ontario, Canada, N6A 5A5

Introduction. Isoflurane is a useful anesthetic agent for neurosurgical procedures and for the production of induced hypotension. Recently Reiz et al, reported that patients with coronary artery disease (CAD) given isoflurane anesthesia may develop ST segment depression indicating myocardial ischemia.[1] The purpose of this study was to investigate the effect of isoflurane induced hypotension on the myocardium of neurosurgical patients as reflected by changes in ECG and cardiac enzymes.

Method. This study was approved by our Ethics Committee and informed consents were obtained. Twenty-one patients were studied, 18 with cerebral aneurysms and 3 with arterio-venous malformations (AVM). A standard 12-lead electrocardiogram (ECG) and cardiac enzymes (CPK, LDH and isoenzymes) were obtained preoperatively. Patients were unpremedicated and anesthesia was maintained with fentanyl, isoflurane, pancuronium and nitrous oxide. ECG (lead II) and a 2-channel Holter monitor (leads V_1 and modified V_5) were monitored intraoperatively. A 12-lead ECG was obtained in the Recovery Room and daily for 3 postoperative days. Intraoperative cardiac enzymes were measured during hypotension, posthypotension and postoperatively q6h for the first 24 hours, q12h for the second 24 hours and once on day 3.

Results. The mean age of the patients was 46±12 yrs. Twelve patients were controlled hypertensives and 2 had a history of CAD. The ECG results are shown in Table I. Preoperative ECG abnormalities included non-specific ST-T wave changes and axis deviation. Holter monitoring showed ischemic changes in 1 patient and arrhythmias in 2. The ECG changes that occurred in the Recovery Room and on postoperative days 1 and 2 consisted of diffuse non-specific ST-T wave changes which cleared by day 3. The mean time of isoflurane induced hypotension was 81.2 min (range 10 to 395 mins). The mean level of hypotension was 49 mmHg (40 to 65 mmHg).

CPK increased in all patients following surgery (Fig. 1) but the increase was CK_3 (skeletal muscle). Isoenzymes LDH_1 and LDH_2 (cardiac) and the ratio LDH_1/LDH_2 (Fig. 2) showed no significant increase.

Discussion. Reiz et al, suggested that coronary steal may occur because isoflurane is a potent coronary vasodilator. However, we are unaware of any evidence of myocardial ischemia or infarction intraoperatively or postoperatively with isoflurane-induced hypotension. In this study with isoflurane-induced hypotension there was no evidence of myocardial infarction by clinical history, ECG or cardiac enzyme measurement. The one patient who did develop ischemia on Holter monitoring during hypotension had no enzyme changes nor further ECG changes.

Of the 9 patients who had subarachnoid hemorrhages 6 patients had abnormal preoperative ECG's. This is consistent with the known observation that many patients with cerebral hemorrhage develop ECG abnormalities which may not indicate myocardial damage. Of interest, there were frequent ECG abnormalities, mostly non-specific ST-T wave cha in the Recovery Room and first postoperative day These patients had no angina and normal cardiac enzymes. The changes seen on the ECG may indicate the effects of cerebral hemorrhage or intracranial surgery. The 2 patients with CAD showed no evidence of ischemia.

We conclude that (1) isoflurane induced hypotension is safe for the myocardium, and (2) ECG ST segment changes may occur postoperatively following vascular neurosurgical procedures which may not be indicative of myocardial damage.

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TABLE I

NUMBER OF PATIENTS WITH ECG CHANGES

Intraop (Lead II)	Holter	Recovery Room	Postop Day 1	Day 2	Day 3
2	3	7	10	1	0

FIG. I

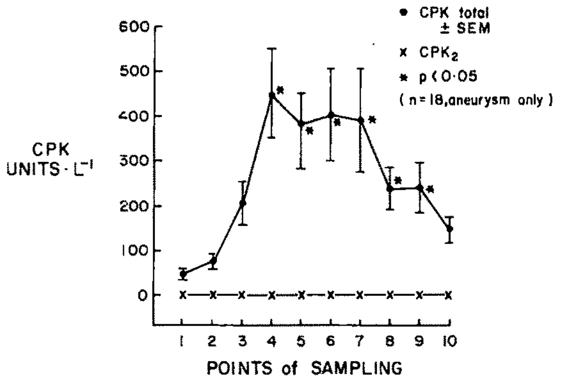
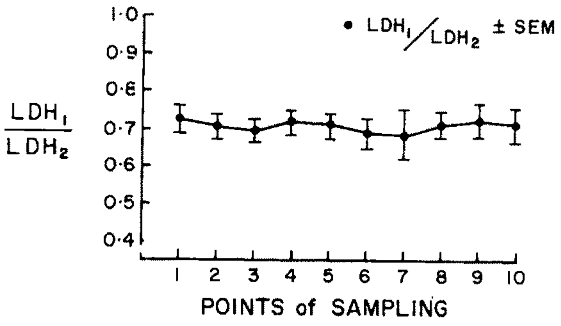


FIG II



Title: CARDIOVASCULAR AND PHARMACODYNAMIC EFFECTS OF HIGH DOSE PANCURONIUM-METOCURINE COMBINATION

Authors: JAJ Martyn, M.D., J. Durant, M.D., S.K. Szyfelbein, M.D., and N.G. Goudsouzian, M.D.

Affiliation: From the Anesthesia Services of the Massachusetts General Hospital, Shriners Burns Institute, and the Department of Anesthesia, Harvard Medical School, Boston, Massachusetts

Introduction. Drug of choice for rapid onset of neuromuscular (NM) paralysis in emergency situations continues to be succinylcholine (SCh). In certain pathological states such as burns and denervation syndromes SCh is contraindicated because of the possibility of a hyperkalemic response,[1] and an alternative is needed.

Higher doses of nondepolarizing NM relaxant can produce rapid onset of NM paralysis in normal patients.[2] Following burns and denervation, the dose and serum concentration requirement of nondepolarizing NM relaxants for effective paralysis is increased two- to threefold.[3] These large doses may cause unacceptable cardiovascular responses. The combination of Pancuronium (Pm) and Metocurine (mTc) causes minimal alterations in heart rate (HR) and blood pressure (BP), while the onset and recovery from NM paralysis is more rapid.[4] In this study we evaluated the cardiovascular and NM pharmacodynamic effects of high dose Pm-mTc combination in acutely burned and reconstructive surgery patients.

Methods. The study was approved by the Human Studies Committee. Thirty-three children 1-17 yrs of age were studied. Fifteen patients with acute burns and 18 recovered burned patients scheduled for reconstructive surgery acted as controls. The clinical variables are summarized in Table 1.

Table 1 Clinical Variables (Mean ± SE)

	Reconstructive	Burns
Age (yr)	9.3 ± 1.3	10 ± 1.1
Weight (kg)	40.2 ± 4.5	43.5 ± 6.1
Time after burn (weeks)	270 ± 52	3.6 ± 1.4
Burn size (%)	-	65.3 ± 6.3

In all patients anesthesia was induced with intravenous (iv) thiopental or rectal methohexital and maintained on $N_2O + O_2$ and narcotic. NM transmission was studied by stimulation of the ulnar nerve by supra maximal pulses of 0.2 ms duration at a frequency of 0.15HZ was used. The thumb adduction was recorded through a force displacement transducer.

Following the establishment of a stable HR, BP, and twitch tension, predetermined doses of Pm/mTC combination were administered. The ED_{95} for Pm/mTC combination in reconstructive surgery and burned patients were 0.015 mg/kg and 0.035 mg/kg of Pm and 0.05 mg/kg and 0.125 mg/kg of mTc respectively.[5] Two and 3 times the ED_{95} doses of the combination of these relaxants were administered (Table 2). The changes in HR and systolic BP were noted at ½, 1, 3, and 5 mins. The time to reach 95% twitch depression and the time for spontaneous recovery from maximal depression to 25% of control twitch height were also noted. The t-test was used to evaluate statistical significance.

Results.

Table 2 Pharmacodynamics

	Reconstructive		Burns	
	2xED_{95}	3xED_{95}	2xED_{95}	3xED_{95}
Dose Pm/mTc (mg/kg)	.03/.1	.045/.1	.07/.25	.105/.375
Time to 95% depression (mins)	4.3±.7	1.84±.4*	3.1±.9	1.3±.2*
Time to 25% recovery (mins)	46±4	86±18	113±18†	152±32†

*$p < 0.05$ 2xED_{95} vs. 3xED_{95}
†$p < 0.05$ burns vs. equipotent dose reconstructive patients

In both reconstructive surgery and burned patients, despite 2xED_{95} doses the time to 95% twitch depression was over three mins. However, the use of 3xED_{95} doses resulted in a rapid onset of twitch depression. In both groups the high doses administered did not result in significant change in HR or BP. For the same equipotent dose administered burned patients had a longer recovery time compared to reconstructive surgery patients.

Discussion. This study documents a technique of administration of nondepolarizing NM relaxants that can produce rapid onset with practically no change in cardiovascular parameters. The 3xED_{95} dose for burned patients is approximately seven times the dose for normal patients. Despite such high doses the cardiovascular changes were minimal. The major disadvantage of this technique is the prolonged recovery time in burned patients, compared to reconstructive surgery patients. The prolonged recovery time may be related to the altered kinetics reported following burns. A dose of 0.105 mg/kg of Pm and 0.375 mg/kg of mTc in combination is a useful alternative to SCh in patients who have a contraindication to SCh and show resistance to nondepolarizing NM blockers.

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Title: THE SENSITIVITY OF END-TIDAL NITROGEN IN THE DETECTION OF LARGE BOLUS VENOUS AIR EMBOLISM IN DOGS

Authors: MJ Matjasko, M.D., JH Hellman, B.S., CF Mackenzie, M.D., M Helrich, M.D.

Affiliation: Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland

Introduction. Previous studies[1] have demonstrated that maximum increases in end-tidal nitrogen (ETN_2) precede maximum decreases in end-tidal CO_2 ($ETCO_2$) during graded low dose (0.25 to 1.0 cc/kg) bolus venous air embolism (BVAE). This study was done to assess the sensitivity of ETN_2 measured by mass spectrometry (MS) during large BVAE (1.0 to 2.5 cc/kg).

Methods. Five preconditioned mongrel dogs (14-20 kg) were anesthetized with IV pentobarbital 30 mgm/kg, intubated, and ventilated with a volume cycled ventilator (Engstrom 312) at an FIO_2 of 1.0 (0.04% N_2 contamination) to maintain $PaCO_2$ between 34-43 mmHg, checked prior to each VAE. Anesthesia was maintained by constant infusion of low dose thiamylal and pancuronium 0.1 mg/kg/h. Maintenance fluids were given at 5 cc/kg/h. A precordial Doppler (PD) was used to monitor flow disturbances. Direct blood pressure and blood gases were obtained from a femoral arterial catheter; a pulmonary artery catheter was inserted to the wedge position and the balloon deflated. A forelimb vein was used for air injection by hand over 5 seconds. One hour of denitrogenation preceded BVAE.

Mean arterial pressure (MAP), pulmonary arterial pressure (PAP), ETN_2, $ETCO_2$ (Medspec II MS) were displayed continuously on a strip chart recorder. Temperature was maintained between 36-37°C. Pressure transducers were calibrated to atmospheric pressure and a 50 mmHg fluid column. The MS was calibrated with 4 gas combinations: room air; 100% O_2; 3.15% N_2, 96.85% O_2; 5.51% CO_2, 3.32% O_2, remainder N_2 (factory calibrated ± 0.03%). The MS sensitivity for N_2 and CO_2 was 0.01% and 0.1% respectively. Calibration of the MS was verified at the end of the experiment and was stable. Baseline (BL) measurements were taken prior to each BVAE (1.0, 1.5, 2.0, 2.5 cc/kg) and 20-30 minutes were allowed for return of all parameters to BL.

Following each BVAE, the time to appearance and magnitude of the peak changes in ETN_2, $ETCO_2$, PAP were observed. $PaCO_2$ and PaO_2 were measured at the time of maximal depression of $ETCO_2$. Changes in MAP, PAP were measured at end-expiration. Intrapulmonary shunt and cardiac output were not measured.

The pooled standard deviation (SD) of the baseline ETN_2 and $ETCO_2$ values was 0.0117% and 0.035% respectively. Changes in ET values after BVAE were considered significant if they exceeded BL values by 3SD. Changes in MAP and PAP were considered significant if they exceeded BL by 25%. The t-test for paired differences was used in data analysis.

Results. Changes in the PD sounds were heard with all air doses in all animals. **ETN_2:** A biphasic pattern of ETN_2 elevation, depression below BL, and return to BL was seen in 4 of 5 animals at 1.0 and 1.5 cc/kg BVAE and in all animals at 2.0 and 2.5 cc/kg. The peak increase in ETN_2 (Δmax) was dose-related and significant in all animals at all air doses (Table 1). The peak decrease in ETN_2 was significant in 4 of 5 animals at 1.0 and 1.5 cc/kg and in all animals at 2.0 and 2.5 cc/kg. The time to Δ max ETN_2 elevation was earlier than Δ max $ETCO_2$ and Δ max MAP after all BVAEs ($p < 0.05$) and was not significantly earlier than Δ max PAP (Table 2). The time to Δmax ETN_2 depression was later than Δ max $ETCO_2$ and Δmax PAP ($p < 0.05$) and was not significantly later than Δ max MAP. **$ETCO_2$:** The Δ max $ETCO_2$ was significant in all animals at all doses (Table 1). The time to Δ max $ETCO_2$ was later than Δmax PAP in all BVAEs ($p < 0.02$) and was not significantly earlier than Δ max MAP (Table 2). **PAP:** The increase in PAP was dose-related and significant in all animals at all doses (Table 1). The time to Δ max PAP was earlier than Δ max MAP in all BVAEs ($p < 0.05$)(Table 2). **MAP:** The decrease in MAP was significant in 2 of 5 animals at 1.0 cc/kg, 3 of 5 at 1.5 cc/kg, and 4 of 5 at 2.0 and 2.5 cc/kg BVAE. The peak MAP decrease was dose-related (Table 1) and at least 19% in all BVAEs.

The animals were not terminated therefore there was no definitive indication that pulmonary and cardiac abnormalities were absent.

Discussion. ETN_2 is more sensitive than $ETCO_2$ and as sensitive as PAP in the detection of large BVAE. Characteristically, ETN_2 and PAP peak simultaneously and precede maximum depression in $ETCO_2$ by approximately 50 seconds at all air doses. Increases in ETN_2 still herald the onset of a large BVAE despite severe cardiorespiratory embarrassment. The return of $ETCO_2$ and PAP and the biphasic ETN_2 values to baseline all confirm the physiologic resolution of the insult. Shared OR mass spectrometers may fail to identify ETN_2 peaks if sampling gaps are greater than 30 seconds. The variations in ETN_2 that occur in normal anesthetized patients and during VAE must be established in the clinic to assess the sensitivity and specificity of ETN_2 monitoring.

References.

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Table 1: Maximum Change (mean ± SD) from Pre-Embolism Control (BVAE)

cc/kg	1.0	1.5	2.0	2.5
ΔETN_2 % — Elevation	0.18 ± 0.09*	0.25 ± 0.13*	0.30 ± 0.16*	0.30 ± 0.11§
ΔETN_2 % — Depression	−0.11 ± 0.08*	−0.06 ± 0.03*	−0.11 ± 0.06*	−0.10 ± 0.05§
$\Delta ETCO_2$ %	−1.6 ± 0.4§	−1.5 ± 0.6§	−1.7 ± 0.6§	−1.7 ± 0.6§
ΔPAP (mmHg)	31.4 ± 8.0§	38.0 ± 10.1§	43.3 ± 8.2§	44.5 ± 5.1§
ΔMAP (mmHg)	−42.2 ± 15.3§	−49.3 ± 34.4*	−67.5 ± 46.8*	−85.4 ± 45.6*

§p < 0.01
*p < 0.05

Table 2: Time to Δmax (mean ± SD) (seconds) (BVAE)

cc/kg	1.0	1.5	2.0	2.5
ETN_2 % — Elevation	34.8 ± 5.3	33.8 ± 14.0	33.2 ± 11.6	31.2 ± 8.2
ETN_2 % — Depression	256 ± 84	270 ± 67	245 ± 126	226 ± 98
$ETCO_2$ %	82.2 ± 16.6	81.5 ± 22.9	74.3 ± 22.9	82.2 ± 17.7
PAP (mmHg)	36.4 ± 27.4	32.6 ± 23.5	27.8 ± 10.0	26.6 ± 10.4
MAP (mmHg)	238 ± 47	102 ± 51	84 ± 41	106 ± 29

This work supported in part by a grant from the Pangborn Fund of the University of Maryland.

Title: COMPARISON OF FENTANYL AND VASOPRESSOR RESPONSES IN CHRONIC DOGS ON IMIPRAMINE VS TRANYLCYPROMINE

Authors: RJ McCarthy, Pharm. D., B Braverman, Ph.D., and AD Ivankovich, M.D.

Affiliation: Department of Anesthesiology, Rush Presbyterian St. Luke's Medical Center, Chicago, IL 60612

Introduction. The recommendation that monoamine oxidase inhibitors (MAOIs) be discontinued at least two weeks prior to elective surgery[1] is widely accepted. Those patients who must be maintained on antidepressant therapy are usually switched from MAOIs to tricyclic antidepressants (TCAs) which are thought to pose less risks of adverse drug interactions. Recently, we have shown that patients on MAOIs may undergo elective surgery without complications.[2] Furthermore, no complications were found in dogs on chronic MAOI therapy subjected to repeated weekly anesthesias with a barbiturate-enflurane-fentanyl-N_2O/O_2 technique plus repeated challenges with norepinephrine and ephedrine.[3] The purpose of this study was to compare the relative hemodynamic responses to fentanyl and vasopressors in dogs who received a MAOI (tranylcypromine) followed by a TCA (imipramine).

Method. Eight male mongrel dogs, 18-25 kg, who were used two months previously for the MAOI study, were anesthetized with amylbarbital, 25 mg/kg IV. Endotracheal tubes were placed and they were mechanically ventilated at 20 ml/kg V_t, 12 b/min., with 3:1 $N_2O:O_2$ and enflurane. After percutaneous catheters were placed and the end-tidal enflurane concentration stabilized at 1% (Engstrom Emma), 500 mcg of fentanyl was slowly injected IV. After 10 minutes, samples for blood-gases and plasma catecholamines were taken. Blood pressure, heart rate, and ECG (lead II) responses to bolus injections of norepinephrine (NE), 0.1 - 0.6 mcg/kg, and ephedrine (EPH), .03 - .12 mg/kg, were recorded. Ten to fifteen minutes after the last EPH injection (approximately 2.5 to 3 hours post fentanyl), all anesthetics were discontinued and the animals were ventilated with room air. The times to arousal were measured. The dogs then received an injection of imipramine, 25 mg I.M., every day for three weeks. The animals were returned to the laboratory once weekly and the above procedure was repeated. After the third week, the TCA therapy was discontinued and the measurements were repeated after the first and fourth week of recovery. Data were compared by ANOVA for repeated measures.

Results. The $\overline{BP}$ after 1% enflurane - N_2O/O_2 anesthesia was not significantly different comparing the control period to the period of TCA treatment or the recovery period; these values were comparable to the observations when the dogs were on an MAOI. The hypotensive response following IV fentanyl was not significantly greater during either MAOI or TCA treatment compared to control. Heart rate changes were not significantly different for the NE challenges, but the peak $\overline{BP}$ responses and the $\Delta\overline{BP}$ were significantly greater during TCA treatment compared to control and recovery periods. The peak $\overline{BP}$ responses when the dogs were on MAOI therapy were not significantly different from control; however, the $\Delta\ \overline{BP}$ was reduced during MAOI therapy because of an increase in baseline $\overline{BP}$. The $\overline{BP}$ duration product (peak $\overline{BP}$ x response duration) was not significantly different and the time for 80% return to baseline was greatest during the control week prior to TCA therapy. The $\overline{BP}$ duration product and the 80% return to baseline were greatest four weeks following discontinuation of MAOIs. One dog, after two weeks of imipramine (TCA) treatment, died because of ventricular fibrillation after receiving 0.3 mcg/kg of NE; no complications were observed during MAOI therapy. Heart rate responses were not different for the EPH challenges, but the peak $\overline{BP}$, $\Delta\ \overline{BP}$, the time to return to 80% of baseline, and the BP duration product were significantly greater during the control and recovery periods compared to the TCA periods. The peak $\overline{BP}$, $\Delta\overline{BP}$, 80% recovery time, and the duration product during MAOI therapy was significantly greater compared to control and recovery periods. The times to arousal were significantly greater during TCA therapy than during control, 9.4±1.6 to 25.1±4.2 seconds, which again was in contrast to the MAOI treatment where arousal times were not significantly different.

Discussion. The results of this study suggest that with our balanced anesthesia technique in dogs, neither MAOI nor TCA therapy resulted in overall adverse responses i.e., hypertension, hypotension, hyperpyrexia or coma. Two important exceptions should be noted: 1) As previous work has shown,[4] TCAs increase susceptibility to lethal arrhythmias. 2) The sedative effect of TCAs may prolong narcotic or barbiturate recovery times. In conclusion, not only were adverse responses to fentanyl or vasopressors absent in dogs chronically treated with an MAOI followed by a TCA, but also there may be greater risk in switching patients from an MAOI to a TCA prior to elective surgery.

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Title: MYOCARDIAL METABOLISM AND HEMODYNAMIC RESPONSES WITH FENTANYL-ENFLURANE ANESTHESIA IN CORONARY PATIENTS.

Authors: AJ McIntyre, M.D., EA Moffitt, M.D., RA Barker, M.B., DD Imrie, M.B., DA Murphy, M.D., R Landymore, M.D., and CE Kinley, M.D.

Affiliation: Departments of Anaesthesia and Surgery, Dalhousie University, Halifax, Nova Scotia, Canada.

Introduction. Both fentanyl[1] and enflurane,[2] given alone with oxygen, have been shown not to be ideal anesthetics for patients having coronary artery bypass grafting (CABG). Even high-dose fentanyl does not always maintain circulatory depression. Enflurane can do the latter but hypertension occurs early on awaking. Induction with fentanyl and subsequent controlled circulatory depression with enflurane is a popular, effective combination. Hence we studied patients having that technique for CABG, to document the correlation of hemodynamics to coronary sinus blood flow (CSBF) and myocardial oxygen and lactate metabolism. Sequential studies were done before induction, 6 times during anesthesia and at 1 and 24 hours afterward.

Methods. Approval from the Ethics Committee and informed consent were obtained. Ten men were typical CABG candidates with ventricular function preserved. Mean age was 60.8 years and weight = 81.4 Kg. Nine had Class III or IV disability; 7 had previous M.I. Mean E.F. = 0.73, C.I. = 2.49 L/min/m^2 and LVEDP = 10 mm Hg. All were kept on beta blockade until operation. After diazepam and morphine (mean 10.5 and 13 mg) and local anesthesia in the O.R., a radial cannula and two thermodilution catheters were inserted (right internal jugular vein): the PA catheter plus a Ganz catheter into the mid CS by fluoroscopy. Each study consisted of determining C.I., CSBF, arterial and central pressures plus arterial and CS samples for O_2, Hb and lactate. After induction with I.V. fentanyl (30 µg/kg) and pancuronium, enflurane-O_2 (average inspiratory concentration 1.60%) was given to reduce B.P. by 25%, for a mean of 10.2 minutes before study 2. After intubation enflurane (up to 2%) was given as needed to maintain B.P. below that awake.

Results (Table). Mean (M) heart rate: stayed slow until postpump. M-mean arterial pressure: no hypertension on intubation; was kept below control during anesthesia. PCW - no change. M-C.I. decreased on induction and remained so until 24 hours later. M-Stroke work I.: decreased throughout. M-SV resistance: no change until sternotomy; also elevated at 1 hour in I.C.U. M-CSBF: decreased after intubation, back to awake level postpump. M-CSO_2 content increased so MVO_2 decreased throughout M-lactate extraction remained normal. M-awaking time = 90 minutes and M-extubating time = 13.5 hours. Two patients required nitroprusside for early post-operative hypertension.

Discussion. In CABG patients with good ventricular function, kept on beta blockade and well-sedated, fentanyl-enflurane provided a smooth induction and controlled maintenance hemodynamically. Autonomic response to intubation was minimal. Cardiac index and stroke work were decreased and heart rate slow; hence MVO_2 likewise lessened. Lactate extraction continued: evidence of continued global oxygen balance. This combination proved to be a highly satisfactory technique.

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*<.001 **<.005 ***<.01 ^{0}<.05 ^{00}<.02 + Mean±S.D.

n = 10	AWAKE CONTROL	POST INDUCTION	POST INTUBATION	POST STERNOTOMY	POST PUMP	ICU	
						1 HOUR	24 HOURS
RATE beats/min.	$59 \pm 7^{+}$	60 ± 7	61 ± 7	56 ± 5	$77 \pm 14_{**}$	$72 \pm 7_{*}$	$77 \pm 11_{*}$
MAP mm Hg	89 ± 13	$65 \pm 13_{*}$	$73 \pm 11_{*}$	$83 \pm 12_{0}$	$76 \pm 10_{**}$	94 ± 11	80 ± 16
PCW mm Hg	11 ± 4	9 ± 4	11 ± 4	8 ± 4	11 ± 4	14 ± 5	9 ± 4
CI L/m/m^2	2.9 ± 0.5	$2.2 \pm 0.5_{**}$	$2.4 \pm 0.6_{0}$	$2.0 \pm 0.3_{*}$	$2.3 \pm 0.9_{0}$	$1.9 \pm 0.8_{00}$	3.0 ± 0.7
SWI gM/m^2	76 ± 19	$40.4 \pm 19_{*}$	$48.3 \pm 19.5_{**}$	$49.3 \pm 16.8_{*}$	$37 \pm 16.4_{*}$	$35 \pm 11_{**}$	$45.6 \pm 14.9_{***}$
SVR d·sec·cm^{-5}	1205 ± 282	1125 ± 282	1164 ± 255	$1676 \pm 336_{**}$	1413 ± 902	$1667 \pm 665_{00}$	1025 ± 322
CSBF ml/min	113 ± 30.9	91.5 ± 30.9	$84 \pm 33_{0}$	$59 \pm 28.6_{***}$	134 ± 55.9	117 ± 52.8	$181 \pm 53.8_{***}$
CS O_2 SATUR. %	36 ± 7	$47 \pm 7_{*}$	$46 \pm 5_{*}$	$42 \pm 2_{*}$	$53 \pm 7_{*}$	$48 \pm 5_{*}$	$49 \pm 5_{*}$
CS O_2 CONTENT	6.4 ± 1.5	$8.3 \pm 1.5_{*}$	$8.2 \pm 1_{*}$	$7.1 \pm 0.6_{**}$	6.3 ± 1.6	7.4 ± 1.5	$7.9 \pm 1_{**}$
MVO_2 ml/min	12 ± 3.5	$8.7 \pm 3.5_{00}$	$7.3 \pm 2.9_{00}$	$5.5 \pm 2.0_{***}$	$7 \pm 3.2_{00}$	$8.2 \pm 3.5_{0}$	12.9 ± 5.3
% LACT EXTRACT %	32 ± 3	28 ± 3	42 ± 20	$44 \pm 9_{**}$	$16 \pm 14_{***}$	$18 \pm 11_{00}$	$9 \pm 14_{**}$

Title: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) FOR THE RELIEF OF PAIN FOLLOWING THORACOTOMY

Authors: J. C. McMichan, M.B.,B.S., W. C. Oliver, M.D., T. R. Holtackers, R.P.T., P. Pairolero, M.D.

Affiliation: Mayo Clinic, Rochester, MN 55905

Introduction: Postoperative pulmonary complications can be caused by depressed pulmonary function associated with incisional pain. Pain relief is therefore important, but it must not produce further complications or depression of pulmonary function. Up to now, TENS has not been available in the intensive care units for analgesia because of the marked interference with cardiac monitoring devices when the stimulating current is applied to the chest wall. TENS produces adequate analgesia following upper abdominal surgery (1) and increased vital capacity following thoracic surgery after discharge from the ICU (2). Therefore, we were instrumental in the development of a TENS unit modified to prevent interference with the electrocardiograph. This study was designed to observe the effects of the modified unit, using two different frequencies of stimulation, on the postoperative parenteral analgesic requirements of patients who had undergone thoracotomy.

Methods: Three groups were studied during a 12 month period. All underwent thoracotomy by the same surgical team and were managed in the postoperative period in the same ICU. Group I--No TENS; control. A retrospective review of the records of patients who underwent thoracotomy, before the modified TENS unit was available. Group II--TENS at 110 cycles/sec. Group III--TENS at 65 cycles/sec. The group details are in Table I.

Table I

	Group I n=45	Group II n=42	Group III n=54
Males/females	26/19	29/13	36/18
Age-yrs Mean±S.D.	57.5 ±17.2	55.3 ±15.4	61.2 ±13.4
Duration stimulation (hrs)		27.1 ±13.0	27.7 ±16.6
ICU stay (hrs)	25.9 ±12.1	28.2 ±18.3	29.2 ±18.8
Hospital stay (days)	8.0 ±7.2	9.2 ±4.4	10.2 ±4.6

Group III patients were significantly older than those in group II (P<0.05), but not compared to Group I which did not differ from Group II. The duration of TENS in the ICU and the lengths of hospital and ICU stay were statistically similar for each group. More patients in Group I received preoperative narcotics (16/45) compared to Group II (7/42; P<0.05), but not compared to Group III (15/54).

The details of surgery are in Table II. With one exception, all patients received a volatile anesthetic agent and all but 7 received narcotic supplementation during the procedure.

Table II

	Number of patients		
	Group I	Group II	Group III
Thoracotomy right/left	31/14	23/19	27/27
Pulmonary malignancy	36 (80%)	23 (55%)	40 (74%)
Pulmonary resection	38 (84%)	31 (74%)	43 (80%)
Pneumonectomy	3 (1%)	7 (2%)	5 (9%)

At the completion of surgery, sterile 6-inch long adhesive electrodes were placed on either side of the entire length of the closed skin incision and covered with the usual dressings. Electrical stimulation was commenced on arrival of the patient in the recovery room at a standard strength of 30 m amps and was continued while effective. Parenteral narcotics were given at the request of the patient or on the judgement of the attending physician that TENS was not supplying adequate analgesia despite adjustment of the delivered current strength. Detailed records were kept of narcotic administration. The amount of narcotics received was standardized such that one analgesic unit was defined as being equivalent to Fentanyl 0.1 mg, Meperidine 75 mg and Morphine 10 mg. The number of analgesic units for each patient was calculated in terms of preoperative body weight. Using unpaired "t" tests for measured variables and Chi square test for observed variables, Groups II and III were compared to Group I and to each other. This study fulfilled the conditions of the institutional human studies committee.

Results: Before and during surgery, Group II received more narcotics (0.072±0.067 units/kg) compared to Group I (0.043±0.04 units/kg; P<0.02) and Group III (0.045±0.059 units/kg; P<0.05). There was no statistical difference between Groups I and III. In the postoperative ICU period, the control Group I (0.045±0.023 units/kg) required more than both Group II (0.032±0.029 units/kg; P<0.05) and Group III (0.018±0.023 units/kg; P<0.001). Also, Group II patients required more narcotics than Group III (P<0.02). One patient in Group I received no narcotics in the ICU. The corresponding number for Group II was 5 and for Group III was 12 (P<0.005 compared to Group I).

Discussion: The parenteral, epidural and intrathecal routes for analgesia are invasive and not without undesired side-effects, complications and technical difficulties. On the other hand, TENS appears to be without complications and is easy to administer. As an initial assessment of its efficacy, this study has shown that TENS reduces narcotic requirements in the immediate post-thoracotomy period and that this reduction is more marked with the slower of the two frequencies of stimualtion studied. It therefore appears that TENS is a modality of analgesia worthy of further study to determine (a) the most beneficial pattern of stimulation, (b) if pulmonary function is improved and (c) if pulmonary complications are less frequent following a decrease in narcotic requirements in the early post-thoracotomy period.

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TITLE: ATRACURIUM AND INTRACRANIAL PRESSURE IN MAN

AUTHORS: M. D. Minton, M.D., J. A. Stirt, M.D., and R. F. Bedford, M.D.

AFFILIATION: Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, VA 22908

Introduction. Safe use of muscle relaxants in patients suspected of having reduced intracranial compliance requires hemodynamic stability and minimal impact on intracranial pressure (ICP). Both succinylcholine (1) and curare (2) have demonstrated the potential to elevate ICP, and curare possesses hemodynamic effects (3) that may further compromise cerebral perfusion. While pancuronium has been shown not to affect ICP (4), its cardiac chronotropic effects are well documented (3) and increases in blood pressure may be deleterious in patients with impaired cerebrovascular autoregulation. The hemodynamic stability associated with atracurium (5), however, suggests potential for use in neuroanesthesia. To date there are no studies to document the effects of atracurium on ICP in humans.

Methods. The subjects of this study were ten consecutive, unpremedicated patients who were free of significant cardiopulmonary disease. Patients were scheduled for elective craniotomy and tumor resection. Preoperative CT scans revealed the presence of supratentorial neoplasms greater than 3 cm diameter in all patients. The study protocol was approved by the institutional human studies committee and informed consent was obtained. A subarachnoid pressure screw, arterial and peripheral venous catheters were placed under local anesthesia and all pressures were continuously transduced and recorded. The zero reference point was the external auditory meatus. After a stable baseline period of intracranial and arterial pressures was observed, intracranial compliance was tested by injection of one milliliter of sterile saline through the subarachnoid bolt. Anesthesia was then induced with thiopental 4 mg/kg IV and 70% nitrous oxide in oxygen. Additional increments of thiopental were administered if necessary to obtund lash reflex or allow control of ventilation by face mask. Constancy of controlled ventilation was monitored with end-tidal CO_2 measurement and verified by arterial blood gas determinations between 1 and 3 minutes before and after atracurium. Following the initial ICP decrement from thiopental, intracranial and arterial pressures were permitted to return to baseline values. Atracurium 0.5 mg/kg was then administered intravenously as a bolus and constant controlled ventilation was continued until 5 minutes after atracurium injection. Adductor pollicis twitch height in response to supramaximal ulnar nerve stimulation at 0.15 Hz was recorded with a Grass force-displacement transducer. Sequential values for ICP and mean arterial pressure (MAP) were compared using a one-way analysis of variance. Arterial pCO_2 levels were subjected to Student's t-test for paired data. $p<0.05$ was regarded as significant.

Results. The patients studied are characterized in Table 1. All patients had evidence to suggest compromised intracranial compliance either by CT scan findings or pressure-volume testing. Study results are summarized in Figure 1. Following atracurium 0.5 mg/kg IV, no significant change in ICP or MAP was detected during the study period, although ICP was found to decrease significantly after thiopental 4 mg/kg IV. Calculated cerebral perfusion pressure (MAP-ICP) did not change significantly after atracurium.

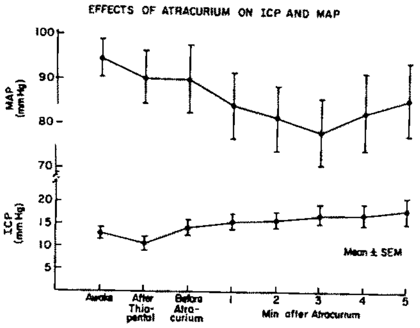
Discussion. Atracurium appears to afford the hemodynamic stability and absence of effect on ICP that are necessary for safe induction of anesthesia in patients with intracranial masses.

Table 1.

CT Appearance of Tumor			Intracranial Compliance	Arterial pCO_2 (mmHg)	
Diameter(cm)	Midline Shift(mm)	Edema(0-3+)*	ΔICP (mmHg/ml)	Before Atracurium	After Atracurium
4.5±0.4	6±2	1.5±0.3	2.2±0.6	38±2	39±2

All values = mean ± SEM
* 0 = No edema, 3+ = edema throughout ipsilateral hemisphere

Figure 1.



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Title: EPIDURAL NALBUPHINE FOR THE RELIEF OF PAIN AFTER THORACIC SURGERY

Authors: MS Mok, M.D.[+], BW Louie, M.D.[‡], BF Hwong, M.D.[‡], KH Chan, M.D.[‡], M Lippmann, M.D.[+]

Affiliation: +Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, California, 90509 U.S.A.
‡Department of Anesthesiology, Veteran General Hospital, Taipei, Taiwan, R.O.C.

INTRODUCTION: The relief of post-operative pain in patients after thoracotomy is of great importance since pain significantly impairs postoperative pulmonary function and early ambulation (1). Epidural administration of morphine has been shown to provide prolonged postoperative analgesia, but being a narcotic agonist it also causes adverse side effects such as intense pruritis, protracted vomiting and at times delayed respiratory depression. Nalbuphine hydrochloride, a potent partial agonist-antagonist narcotic analgesic when administered parenterally has been shown to provide pain relief in a variety of clinical conditions with its potency being similar to morphine and yet less pronounced respiratory depression than morphine (2). The present study was undertaken to evaluate the efficacy and safety of epidural nalbuphine for the relief of postthoracotomy pain.

METHOD: This study was conducted at the Veteran General Hospital after institutional approval and informed consents were obtained from all the patients prior to their entry into the study. Thirty adult patients scheduled for elective thoracic surgeries were enrolled in this study. On the day of surgery, all the patients received thiopental induction and enflurane-N_2O-O_2 for maintenance of anesthesia. At the completion of surgery, while the patient was still in the lateral position under general anesthesia, an indwelling epidural catheter was inserted through either T_{6-7} or T_{7-8} interspace and securely taped in place. In the postoperative period, when the patients had fully recovered from the effect of anesthesia and complained of severe pain, they were divided into 2 equal groups in a randomized double blind fashion. Group A received epidural administration of nalbuphine 10 mg in 10 ml normal saline and group B, serving as control, received epidural normal saline 10 ml. Patient's pain intensities were evaluated by visual analogue scales at 5, 10, 15, 30 minutes and at 1, 3, 6, 12, 24 hours after drug administration. Any patient who did not obtain adequate pain relief after one hour postdrug was given a "rescue" medication of meperidine 1 mg/kg I.M. Vital signs, complaints of side effects and the number of doses of the I.M. analgesic requested were recorded throughout the 24-hour observation period.

RESULTS: The demographic distribution and initial pain intensities were similar for both groups. There is a statistically significant difference ($P < 0.05$) in pain scores between the two groups up to 9 hours (Figure). Onset of pain relief with epidural nalbuphine appeared at the 5 minute observation period, peaked between 10-18 minutes with a duration of action ranging from 4-20 hours (average - 9.2 hours). In the first 9 hours only 2 patients (18%) in group A, whereas 12 patients (80%) in group B required I.M. analgesics with an accumulative dose frequency of 3 for group A and 16 for group B respectively. No evidence of sensory, motor or autonomic blockade were observed in any patient. Incidence of adverse side effects were quite similar in both groups, with drowsiness being the predominent side effect, and no pruritis or respiratory depression being observed in any of the patients. (Table)

DISCUSSION: In a previous study comparing the analgesic effect of five different agents by intrathecal administration, we found that intrathecal nalbuphine 0.4 mg provided significant reduction of postoperative pain, comparable to that of an equipotent dose of morphine and meperidine (3). When applied epidurally in this study, nalbuphine appears to provide excellent pain relief with minimal side effects. The duration of analgesia averaged 9.2 hrs. which is comparable to that of epidural morphine, 5 mg, for postthoracotomy pain as reported by El-Baz, et al (4). However, there is a remarkable low incidence of adverse side effects associated with epidural nalbuphine in our study when compared with those reported with epidural morphine. In our search to provide effective spinal narcotic analgesia with reduced incidence of adverse side effects, nalbuphine holds promise as a desirable alternative to morphine and its role for this clinical application awaits further investigation

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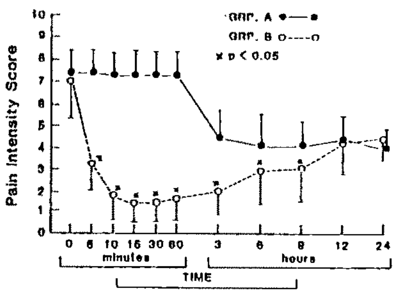
Figure 1: Average Pain Score



TABLE

Incidence of Side Effects

	Grp. A	Grp. B
Drowsiness	7/15	9/15
Nausea	2/15	3/15
Vomiting	0	1/15
Pruritus	0	0
Urinary Retention	1/15	2/15
Urticaria	0	0
Respiratory Depression	0	0

Title: THE COMBINED USE OF ATRACURIUM AND PANCURONIUM FOR THE PRODUCTION OF SURGICAL RELAXATION

Authors: H Nagashima, M.D., HD Nguyen, M.D., S Lee, M.D., R Kaplan, M.D., FF Foldes, M.D., D Duncalf, M.D.

Affiliation: Departments of Anesthesiology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York 10467

Introduction. The administration of the intubating dose of atracurium (ATRC) in 2 increments eliminated the two most significant drawbacks, namely the relatively slow onset of action and the dose related histamine releasing effect of this relaxant(1). With this technique, ideal muscular relaxation, with rapid spontaneous recovery of neuromuscular (NM) transmission and easy reversibility of residual NM block, can be achieved for operations of up to 100 min duration with 1 ampoule (50 mg) ATRC. For longer surgical procedures, where more than 1 ampoule is needed, cost becomes an important factor. This study was designed to combine ATRC and pancuronium (PANC) so that their side effects would be reduced and muscular relaxation for long procedures could be provided at a reasonable cost.

Methods. Thirty-five adult, surgical patients of both sexes signed informed consents to participate in this study, approved by our Institutional Review Board. After premedication with diphenhydramine and meperidine, anesthesia was induced with droperidol, thiopental and fentanyl and maintained with N_2O-O_2 and increments of fentanyl. After induction, the isometric twitch (P) of the adductor pollicis muscle, elicited by stimulation of the ulnar nerve at 0.1Hz, was continuously recorded. At specific times the muscle was stimulated by trains of four 2Hz impulses. All patients first received IV 75 µg/kg "priming" and 6 min later a 250 µg/kg "intubating" dose of ATRC. Intubation was performed when P decreased to about 20% of control. The time between start of injection of the intubating dose and intubation (Intubation Time), the maximal effect and return of P to 25% of control (Clinical Duration) were determined and intubating conditions were assessed. In group I (15 patients), when P returned to 25% of control after the intubating dose of ATRC, relaxation was maintained with PANC. The first maintenance dose of PANC was 25µg/kg and those of subsequent doses 15µg/kg, except that the last maintenance dose was 50 µg/kg ATRC. In group II (20 patients) 100 µg/kg increments of ATRC were injected whenever P returned to 25% of control. After the last dose of ATRC the time for the recovery of P from 25% to 75% of control (Recovery Time) was noted. Residual neuromuscular (NM) block was antagonized by the IV injection of 10 µg/kg atropine followed by 0.5 mg/kg edrophonium.

Results. Intubating conditions were equally satisfactory in both groups at the times indicated in the table. The maximal effect of the initial dose was very similar. The clinical duration of the intubating dose was also similar in the 2 groups. The duration of the first maintenance dose was longer in group I, that received PANC, than in group II. The clinical duration of subsequent maintenance doses, however, was similar in both groups. Recovery rate was shorter in group II than in group I. Before reversal, T4/T1 was smaller in group I than in group II, but there was no difference in T4/T1 following the administration of edrophonium. No significant changes in heart rate or blood pressure were observed in either group before intubation or in group I after maintenance doses of PANC.

Discussion. The described method, consisting of the use of ATRC at the start and the end of anesthesia and maintenance of relaxation in between with PANC, retained the advantages and eliminated the disadvantages of both agents. Satisfactory conditions for tracheal intubation developed within 1.5 min. The clinical duration of the first maintenance dose of 25 µg/kg PANC was about 30 min and that of subsequent 15 µg/kg maintenance doses, about 20 to 25 min were similar to that of 100 µg/kg ATRC. The preliminary administration of ATRC appears to increase the neuromuscular effect of PANC and vice versa. Because of this the last dose of ATRC, administered after PANC should be 50 µg/kg, half of the usual maintenance dose. Following the last dose of ATRC, spontaneous recovery proceeded rapidly and residual NM block could be antagonized equally well by edrophonium in both groups. In conclusion, for operations of more than 100 min duration equally good muscular relaxation, free of side effects, can be provided by the combined use of ATRC and PANC, at a much lower cost, than with ATRC alone.

	GROUP I (n=15)	GROUP II (n=20)
Priming Dose(µg/kg)	75	75
Intubating Dose(µg/kg)	250	250
Intubation Time(min)	1.2±0.1[1]	1.4±0.1
Maximal Block(%)	97.4±0.8	98.9±0.4
Clinical Duration		
Intubating Dose	28.0±1.6	30.7±1.6
1st Maintenance Dose[2]	29.7±9.5*	18.3±0.7
Last Maintenance Dose	23.9±2.6	19.8±1.0
Recovery Rate	18.9±2.2	13.1±1.0*
T4/T1 Ratio		
Before Antagonist	0.44±0.04**	0.58±0.03
2 min after Antagonist	0.90±0.03	0.88±0.03

1. Mean ± SEM
2. Maintenance doses in group I: first 25 µg/kg, subsequent 15 µg/kg PANC, last 50 µg/kg ATRC; in group II all maintenance doses 100 µg/kg ATRC.

* and ** indicate difference between the 2 groups at the p <0.001 and 0.05 levels respectively.

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Title: HEMODYNAMIC INTERACTIONS OF MODERATE DOSES OF FENTANYL WITH ETOMIDATE AND KETAMINE

Authors: IR Newsome, MD, CC Moldenhauer, MD, CC Hug, Jr. MD, PhD, DM Nagle, MMSc, and PE Curling, MD

Affiliation: Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia 30322

Introduction: The use of fentanyl (F) *alone* as an anesthetic is recommended because of the cardiovascular depression that occurs with the addition of diazepam or nitrous oxide.[1] Supplements to narcotic anesthesia are desirable to ensure unconsciousness, to decrease narcotic dosage, and to allow rapid recovery. Etomidate (E) is a hypnotic noted for its lack of cardiovascular effects when given alone or along with low doses of F.[2] Ketamine (K) is a sympathomimetic anesthetic when used alone. The prior administration of F may obtund the sympathetic actions of K so that the combination of F and K may result in minimal hemodynamic changes. This study was designed to investigate the hemodynamic interactions of moderate doses of F with E or K.

Methods: After giving informed consent to the institutionally approved protocol, 14 patients undergoing elective aorto-coronary artery bypass surgery (with left ventricular ejection fraction ≥ 45%) were studied. The majority of patients were taking beta-blockers (n=10), calcium entry blockers (n=11), and nitrates (n=11). The last doses were given the morning of surgery. Patients were premedicated with morphine sulphate 0.15 mg/kg and scopolamine 0.3 mg/70 kg IM 90 min prior to induction of anesthesia. Leads II and V_5 of the EKG, and radial and pulmonary arterial pressures were monitored continuously in all patients. Ringer's lactate 8-10 ml/kg was infused intravenously, when necessary, to maintain a pulmonary capillary wedge pressure (PCWP) ≥ 10 mmHg prior to the induction of anesthesia. Patients were randomly divided into three groups. After metocurine (2 mg/70 kg), all patients were given F50 μg/kg as a 10 min continuous infusion. This was followed by K 1.5 mg/kg given over 60 sec in Group FK (n=5), E 0.3 mg/kg over 60 sec in Group FE (n=5); and no additional anesthesia in Group F (n=4). Rigidity was treated with succinycholine as a bolus (20-40 mg) followed by a continuous infusion (5 mg/min) until the completion of endotracheal intubation. Hemodynamic measurements were obtained prior to induction (C), and 3 min after: F 50 μg/kg, E or K, and after intubation (T). Measurements included heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), PCWP, and arterial blood gases. Systemic vascular resistance (SVR) was calculated. Statistical methods consisted of two way analysis of variance utilizing Tukeys' W test and a three group repeated measures analysis of variance. $P \leq 0.05$ was considered statistically significant.

Results: The addition of E to moderate dose F resulted in statistically significant decreases in MAP, HR and CO (Figure, mean ± SEM) without any changes in filling pressures. SVR also decreased but was not statistically significant. K, however, resulted in minimal changes in hemodynamics when added to moderate dose F. There were no reports of recall of intraoperative events, nightmares or hallucinations in any group. One patient in Group FE remained responsive and breathing after a total F 50 μg/kg. He lost consciousness with the administration of E. Normocarbia was verified at every sampling interval.

Discussion: The addition of E to F anesthesia produced decreases in MAP and CO similar to those reported for diazepam or N_2O. K supplementation of F anesthesia, however, produced no significant hemodynamic changes. The prior administration of F prevented the sympathomimetic responses normally seen during induction with K alone. The combination of fentanyl-ketamine anesthesia may represent an alternative with minimal cardiovascular interactions compared to other fentanyl-hypnotic combinations.

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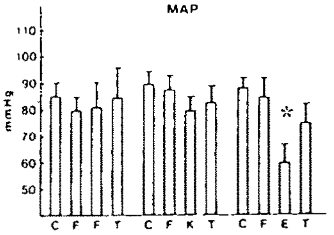
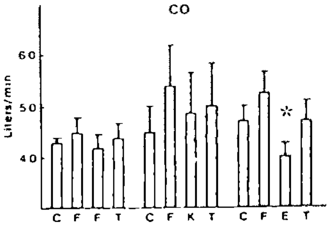
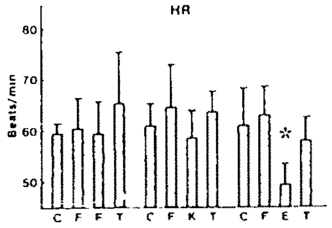




Data presented as mean±SEM

* p < 0.05



Title: THE ROLE OF THE ENZYMATIC HYDROLYSIS OF ATRACURIUM IN VIVO

Authors: V Nigrovic, M.D., M Auen, A Wajskol, M.D.

Affiliation: Department of Anesthesiology, Medical College of Ohio, Toledo, Ohio 43699

Introduction. Hofmann elimination was postulated to be the major route of in vivo degradation of atracurium (Atc); alternatively, hydrolysis of the ester linkage, either spontaneous or enzymatically catalyzed, was also considered possible (1). Since the end-products of Hofmann elimination, i.e., acrylates, were considered potentially toxic (2) whereas those of hydrolysis were not, we considered it important to determine the extent of in vivo degradation of Atc by Hofmann elimination (HE) relative to that by ester hydrolysis (EH). Our working hypothesis was based on the premise that the role of the enzymatic hydrolysis in the overall degradation of Atc in vivo can be uncovered if the inhibition of the putative enzyme - carboxylesterase - produces a prolongation of action of Atc. Indirectly, such a result would imply (a) a lesser role for HE than was previously thought, and, hence, (b) a decreased chance for the formation of potentially toxic products of this elimination reaction.

Methods. In rats (3) and mice (4) triorthotolyl phosphate (TOTP) was demonstrated to effectively inhibit carboxylesterase - the enzyme group thought to catalyze the hydrolysis of Atc (1). Our study was therefore conducted in rats pretreated either with TOTP (125 mg•kg^{-1} i.p.) or its solvent corn oil (1 ml•kg^{-1} i.p.) 18 to 20 hours prior to the actual experiments. Under pentobarbital anesthesia (50 mg•kg^{-1} i.p.) a tracheal cannula was inserted and the animal was ventilated mechanically; the right femoral artery was cannulated for arterial pressure monitoring and the adjacent vein for constant infusion (0.9% NaCl at 0.1 ml•kg^{-1}•min^{-1}) and drug administration. The distal end of the left gastrocnemius tendon was severed and attached to a force transducer. The ipsilateral sciatic nerve was cut and its peripheral end stimulated supramaximally by a bipolar platinum electrode (2 Hz for 2 sec at 10 sec interval). We recorded the systemic blood pressure and isometric contractions of the muscle. After approximately one hour stabilization, rats (in subgroups of 4) were randomly assigned to treatment with Atc (1.2 mg•kg^{-1} i.v.) or d-tubocurarine (dTc, 0.15 mg•kg^{-1} i.v.); in preliminary experiments these doses of the relaxants had been determined to be the minimal doses required to produce a larger than 97% inhibition of the first twitch in the train of four stimuli. From the recordings the following variables were determined: (a) Onset time (time, in seconds, to the maximal inhibition of the first twitch); (b) Duration of the complete relaxation (time in seconds from injection to 10% recovery of the first twitch); and (c) The rate of recovery (the recovery of the first twitch during the initial two to five minutes - expressed in percent of the control height - per minute).

Results. Our data show that the inhibition of carboxylesterase had no influence on the skeletal muscle relaxation produced by dTc whereas it approximately doubled the duration of action of Atc (from 210 sec to 506 sec, $P < 0.01$) and halved the rate of recovery of Atc-induced paralysis (from 34.5 to 16.1 % min^{-1}, $P < 0.01$). The onset of muscle relaxation was not influenced by TOTP for either relaxant.

Discussion. Our data confirmed that in normal, untreated rats - as was observed in all other species studied thus far - Atc, in comparison with dTc, (a) has a much shorter duration of action, and (b) allows for a faster rate of recovery from skeletal muscle relaxation. In the present study, we demonstrate that the enzymatic hydrolysis is an important mechanism of biodegradation of Atc; indeed, inhibition of the enzymatic degradation of Atc prolonged its duration of action so much that the pharmacodynamic parameters (duration of action and the rate of recovery) became indistinguishable from those of dTc.

We conclude that in rats Hofmann elimination does not represent a major metabolic pathway. If these findings can be confirmed for humans, the potential adverse effects from the end-products of Hofmann elimination would be lessened.

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Title: EFFECTS OF THE MECHANICAL VENTILATION ON THERMODILUTION CARDIAC OUTPUT MEASUREMENTS IN MAN

Authors: K. Okamoto, M.D., T. Komatsu, M.D., R. Bhalodia, M.D., K. Kubal, M.D., K. Shibutani, M.D.

Affiliation: Department of Anesthesiology, New York Medical College - Westchester County Medical Center,
Valhalla, New York 10595

Introduction: Measurements of cardiac output (CO) by using thermodilution technique varies considerably even in hemodynamically stable individuals. This variation of CO related to artificial ventilation has been studied in pigs (1) and dogs (2). However, it has not been clear whether the similar pattern of the variation can be observed in patients undergoing coronary artery surgery (CAS). In addition, the role of periocardium on this variation has not been examined. The purposes of this study were: (1) to examine the relationship of thermodilution CO values with the ventilation cycle before sternotomy and after opening of the pericardium; and (2) to determine the most appropriate moment of injection in patients undergoing CAS.

Method: Twenty-four adults patients were studied after institutional approval. 7 Fr. pulmonary artery balloon flotation catheters (Edwards Laboratories) were placed before induction. Its' thermistor lead was connected to a cardiac output computer (Gould Model IM 1044). Anesthesia was maintained with high-dose fentanyl. Pancuronium was given to assure complete muscle paralysis. The patients were ventilated with air-oxygen mixture with a constant volume at a rate of 8 - 11/min. The ventilation volume was adjusted to maintain $PaCO_2$ within normal range. Thermodilution measurements of CO were performed before sternotomy and after opening of the pericaridum, using an injection of 10 ml dextrose (5%) at room temperature, when blood pressure, heart rate and peak airway pressure were stable without surgical stimulation. Injections were made at each of the five phases of the respiratory cycle: I1, begining of inspiration; I2, mid-inspiration; I3, end of inspiration; E1, early mid-expiration; E2, late mid-expiration. The order of the five injections in each series was performed at random. The thermal curves were always monitored. Data analysis: The mean value of cardiac output was calculated from five measurements of each series and taken as the 100 % value. Each measurement was expressed as a percentage of this mean value. Moreover, in each series a mean value of 2 or 3 phases was compared to mean value of the 5 phases of each series. Statistical analyses were performed by using paired and unpaired t-test.

Results: (1) The 25 series of CO measurements were performed before sternotomy. The mean values of peak airway pressure and central venous pressure were 13±3 cmH_2O and 6±2 mmHg, respectively. The variations of CO observed during ventilation cycle are shown in Figure 1. The highest mean value of CO was observed at I2 (108±8 %). The lowest mean value was observed at E2 (90±11 %). (2) The 15 series of CO measurements were performed after opening of the pericardium. The mean values of peak airway pressure and central venous pressure were 13±2 cmH2O and 5±2 mmHg, respectively. The pattern of CO variations observed during ventilation cylce was similar to the pattern before sternotomy. The highest mean value of CO was observed at I2 (105±7 %). The lowest mean value was observed at E2 (96±6 %). (3) The mean value CO from the combination of 2 phases that had the least deviation was the I2-E2 combination (99.6±4.3%). When the 3 phase combinations were compared, the following combination showed the least deviations; I1-I2-E2 (100.4±2.5%), I1-I3-E1 (100.3±2.8%), I1-I3-E2 (99.3±2.5%), I2-I3-E2 (100.9±2.8%)

Discussion: The pattern of CO variations modulated by respiratory cycle was demonstrated. There were no apparent significant changes in the pattern following the opening of the pericardium. The recognition of the respiratory-induced flactuations is important in minimizing the variations of CO in patients undergoing cardiac surgery. These findings suggest that at least two measurements of CO should be made at the different phase of the ventilation cycle to obtain the accurate mean value of CO.

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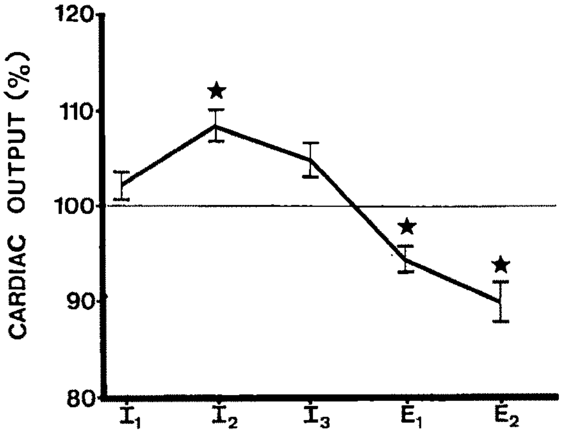

Figure 1. Variations of cardiac output during the ventilation cycle
★ $p<0.05$ as compared to I1 (paired t test)

Title: EPIDURAL ANESTHESIA IN PATIENTS WITH PREVIOUS LUMBAR LAMINECTOMY OR SPINAL FUSION

Authors: Woo Young Park, M.D., Sae J. Kim, M.D. and Thomas E. Macnamara, M.B., Ch.B.

Affiliation: Department of anesthesiology, Veterans Administration Medical Center and Georgeown
University Hospital, Washington, D.C. 20422

Introduction. Spinal anesthesia can be administered safely and effectively for surgery in patients who have had a lumbar laminectomy or spinal fusion (1). Epidural anesthesia, however, is seldom used for surgical anesthesia in post laminectomy patients because of concern that any adhesions in the epidural space resulting from the laminectomy might interfere with the uniform spread of local anesthetic solutions and cause a patchy surgical anesthesia. Some anesthesiologist have also expressed a fear that an epidural block could initiate or exacerbate neurological problems in patients with previous surgery in the spine. There are, however, no data available to support these contentions. This study was, therefore, designed to evaluate the efficacy and safety of epidural anesthesia for surgery in patients with previous lumbar laminectomy or spinal fusion.

Methods. Twenty-two adult male patients who had a past history of lumbar laminectomy or spinal fusion, and who required epidural anesthesia for the proposed surgery were investigated. Institutional approval for the project and informed consent from each patient were obtrained. A #17 Tuohy epidural needle was introduced into the intervertebral space just above the surgical laminectomy scar and the epidural space identified by using loss of resistance technique. With the level of the needle pointing cephalad, 10-20 ml of either 0.5% bupivacaine or 1.5% lidocaine, both with epinephrine (1:200,000), were injected and an epidural catheter inserted. The extent as well as the uniformity of sensory anesthesia on both sides were carefully checked by pinprick every 10 minutes for 30 minutes. The patient's response to surgical stimulation was also noted. Patients who had persistent radicular pain following previous laminectomy or spinal fusion were given 40 mg of methylprednisolone through the epidural catheter at the end of surgery. Postoperatively, patients were questioned regarding any recurrence or any change in character or intensity of their neurological symptoms.

Results. The mean age of the patients was 61 years and mean height 176 cm. Seventeen of the 22 patients had the epidural needle inserted into either 1st or 2nd lumbar intervertebral space. The other 5 patients had the needle inserted into 12th thoracic or 3rd lumbar intervertebral space. Eighteen patients had had a previous lumbar laminectomy and 4 patients had a previous spinal fusion. Thirteen patients received 0.5% bupivacaine and 9 patients 1.5% lidocaine, both with freshly added epinephrine (1:200,000). The mean anesthesia level achieved was T_5. Anesthesia was satisfactory for the proposed surgery (Table I) in all but two patients. One patient failed to have any analgesia, while the other patient complained of slight discomfort upon surgical manipulatin of hip joint, for which 50% N_2O was administered with satisfactory relief of discomfort. Two patients who had persistent radicular pain following their laminectomy, and who were given 40 mg of methylprednisolone through the epidural catheter at the end of surgery noted to have excellent relief of the pain for several days postoperatively. There were no significant intra or postoperative complications attributable to the epidural anesthesia and in no case was there any exacerbation of previous neurological symptoms.

Discussion. One of the twenty-two patients in our study had no anesthesia at all. In this case the local anethetic was most certainly injected outside the epidural space. All other patients had uniform and solid anesthesia to pinprick over the area of the spinal segments invovled in a previous lumbar laminectomy or fusion.. Adhesions formed following lumbar laminectomy or fusion could inhibit the spread of an anesthetic drug within the epidural space thus preventing the drug from acting on spinal nerves at this site. However, on the basis of our findings, it is evident that the absorption of the drug into the cerebrospinal fluid and its leakage out into the paravertebral spaces provide adequate sites of action for good epidural anesthesia. The results of our study further indicate that epidural anesthesia is both safe and effective in patients who have had surgery on the lumbar spine. Thus no surgical patient whose age or physical status would warrant an epidural anesthesia need be denied the advantages of this form of anesthesia because of a previous laminectomy or fusion.

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Table I: TYPE OF SURGERY PERFORMED UNDER EPIDURAL ANESTHESIA

Type of surgery	Number of patient
Transurethral resection of prostate	4
Above or Below knee amputation	4
Total hip replacement	3
Femoropopliteal bypass & graft	3
Surgery in the perineum	3
Others	5

Title: PREANESTHETIC CHECKLIST

Authors: D.A. Paulus, M.D.; J.W. Basta, M.D.; H. Klie; and E.A. Radson, R.N.

Affiliation: Dept. of Anesthesiology, Univ. of Fla. College of Medicine, Gainesville, FL 32610; Holy Cross Hospital, Ft. Lauderdale, FL, 33308; Ohmeda Anaquest Inc., Atlanta, GA, 30360

Introduction. A failure to check equipment before anesthesia has been cited as an associated factor in 22% of critical incidents reported (1). A thorough, routine preanesthetic check of equipment and drugs has been suggested as a possible remedy (2). We developed a checklist of what we thought were essential items and compared it with items that were actually inspected in preparation for anesthesia.

Methods. A thorough checklist containing 48 items was developed (Table 1). Thirty residents from a three-year training program were selected. Experience levels varied with 5 first year (PG-1), 12 second year (PG-2), and 13 third year (PG-3) residents selected for study. One of the residents had prior training and experience as a nurse anesthetist. Each resident was allowed to check and prepare the equipment as usual. After that a research nurse asked each resident to describe the preanesthetic check and simulate it by pointing to the pertinent items on the anesthesia machine. The nurse recorded on the checklist the items that were inspected as they were indicated by the resident. Residents were given percentage scores according to the number of items that had been inspected compared with the total number of items on the checklist.

Results. Raw percentage scores ranged from a low of 70.8% to a high of 95.8% with a group mean of 85.4% and a standard deviation of ± 5.51. Of 48 items on the checklist, 21 (43.7%) were inspected 100% of the time and 27 (56.3%) were disregarded at least once. Of these 27, 14.8% were related to anesthetic supplies and equipment and 85.2% were machine related. Of the items listed, 25.9% were not inspected by 10 residents and 48.1% by 5 residents. Twenty percent of PG-1s (n = 5), 16.6% of PG-2s (n = 12), and 15.8% of PG-3s (n = 13) scored less than 80% (Table 2). Most participants consistently inspected all those items related to airway maintenance and hemodynamic stability.

Discussion. The overall percentage of items not inspected by subjects in this study seems to support that remembering all the necessary elements of a thorough equipment check is difficult. The majority of items disregarded related to the anesthesia machine itself. Comments from residents indicated a false sense of security regarding its proper function and the availability of certain equipment. A secondary finding of this study indicates that training and experience does influence the thoroughness and consistency of preanesthetic checks. A higher percentage of PG-1s scored less than 80%. This may reflect the time required to learn a complex repetitive routine or to gain experience, that is, the relationship of time in training to personal involvement in a mishap. Most participants with higher scores admitted to improvement in routine after a "close call" related to machine failure or equipment inadequacy. We feel this study indicates that an accurate check of anesthesia machine and equipment cannot be done without some form of aid. Because of this and a false sense of security, more stringent preanesthetic checking is required to prevent anesthetic mishaps.

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Table 1. Areas Covered by Preanesthetic Checklist

Monitors	ECG, blood pressure, stethescopes: precordial and esophageal, temperature, gas meter
Anesthesia machine	O_2 and N_2O: central line, connections to wall and machine, tank pressure, flow meter bobbin, flush function Common gas outlet to circle system Anesthetic circle: soda lime, hoses and bag, valve discs, mask Ventilation: power connection, parameters set, connection to anesthesia circuit, testing Vaporizers: fluid levels and filling valves Suction Scavenging system
Anesthetic equipment and supplies	Induction agent, muscle relaxant, vasopressor, atropine, oral airway and tongue blade, endotracheal tube size, cuff, laryngoscope and space blade, stylet, tape, fluids

Table 2. Percentage of Score According to Year of Training

Year of Training	< 80% (n = 5)	80–90% (n = 22)	> 90% (n = 3)
First (n)	1	4	-
Second (n)	2	9	1
Third (n)	2	9	2

Title: WAITING TIME ALTERS INHIBITION OF SUCCINYLCHOLINE FASCICULATIONS BY ATRACURIUM

Authors: A.C. Pinchak, Ph.D., P.E., M.D., J.C. Sung, M.D., J.F. Hagen, B.A., and F. Hall

Affiliation: Departments of Anesthesiology and Mechanical-Aerospace Engineering
Case Western Reserve University, Cuyahoga County Hospitals, Cleveland, Ohio 44109

Introduction Clinical circumstances often alter the waiting time which elapses between the injection of an anti-fasciculation drug, and the time of injection of succinylcholine given for endotracheal intubation. We investigated how the waiting time changes the effectiveness of atracurium, curare and pancuronium in blocking muscle fasciculations caused by succinylcholine.

Methods This study was approved under a monitoring protocol, submitted to the Human Investigation Committee of our institution. A total of 500 subjects were entered into this study and they ranged in age from 5 to 87 years. Members of both sexes were included. A standard dose of 5 mg atracurium, 1 mg pancuronium or 3 mg of curare was utilized for most patients. These doses were administered independent of patient size over the weight range of 50-90 kg. Patients outside this range received a proportioned dose based on their body weight (atracurium, .07 mg/kg, pancuronium, .014 mg/kg and curare, .043 mg/kg). The time was carefully recorded when the non-depolarizing drug was injected and routine clinical procedures followed. Induction proceeded with sodium pentothal (2 to 3 mg/kg) until the patient was unconscious and the depolarizing muscle relaxant succinylcholine was then given. The standard dose of succinylcholine was 100 mg I.V. except for those patients less than 50 kg or greater than 90 kg in weight. Patients outside this weight range received 1.5 mg/kg. After the succinylcholine was injected the waiting time was recorded and the patient was carefully observed for any signs of fasciculation. Fasciculations were described as not present, minimal if slight twitching occurred, or moderate to severe, depending upon the total amount of muscular motion observed. Patients were then divided into various categories depending upon sex, age, and waiting time between injection of non-depolarizing drug and succinylcholine. Percentages of patients fasciculating were calculated for each of these categories and for the overall categories with respect to age. Confidence limits and comparisons between proportions were evaluated according to the methods outlined by Dixon and Massey.[1]

Results A portion of the results may be seen in Fig. 1. All drugs are more effective in blocking fasciculations as the waiting time increases to the 4.5 to 5.0 minute range. At times greater than 5 minutes there may be a loss in drug effectiveness in preventing fasciculations. Additional data are required to evaluate this hypotheses. There are definite differences in the overall fasciculation frequencies for the three drugs, atracurium and curare both had a 15% fasciculation rate compared to a 36% rate with pancuronium. Table I shows that atracurium and curare have a similar effectiveness in preventing fasciculation. Both of these drugs are superior to pancuronium in this regard. The confidence limits shown in Table I indicate no overlap between pancuronium and the other two drugs. A number of other hypotheses were also tested. The data suggested that in the below 30 age range and in the 31-60 year old group, there were sex differences in fasciculation rate; a larger percentage of males fasciculated than females. In the over 60 age group these differences appeared to diminish. However, these impressions were not substantiated by statistical testing. The sex difference results for all ages were almost significant at the 5% level. The waiting time interval between drug injections varied quite considerably in our clinical setting. In the majority of cases the waiting time is between 2 and 3½ minutes. However, there is an appreciable percentage of cases (15%) having a waiting time greater than 5 minutes. The overall difference demonstrated here between pancuronium and curare agrees with the findings of Blitt and co-workers.[2] They kept a fixed interval of about 3.5 min for the waiting time and found that pancuronium appeared to be somewhat less effective than curare or metacurine in the prevention of fasciculation inhibitions. Our results for all 3 drugs demonstrate that the anti-fasciculation effect is strongly dependent upon the waiting time. For optimum inhibition of fasciculations a waiting time of 4 to 5 minutes should be utilized.

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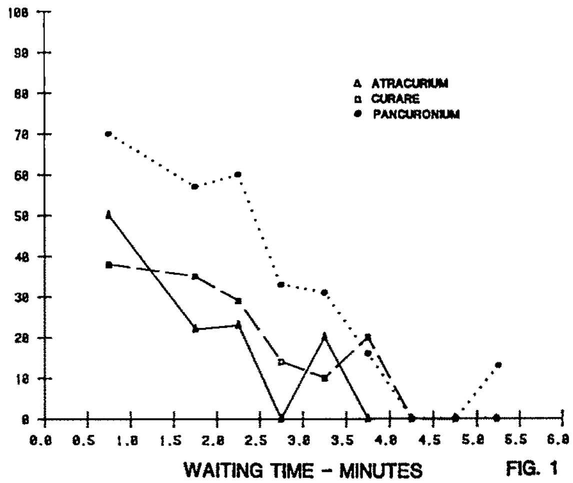

FIG. 1

Figure 1: Waiting time effect on inhibition of succinylcholine induced muscle fasciculations. Values for 5.0 to 5.5 minute range include all waiting times greater than five minutes. Values for 0.5 to 1.0 minute range include all waiting times less than one minute.

Table I Overall Proportion of Patients Fasciculating
($\bar{X}$ = X/N)

Drug	Atracurium	Curare	Pancuronium
N	54	228	218
$\bar{X}$ (%)	15	15	36
C.L. Lower	.05	.10	.30
C.L. Upper	.25	.20	.42

X = number fasciculating, N = number of patients in sample
C.L. = 95% confidence interval

Title: CARDIOVASCULAR AND PERIPHERAL BLOOD FLOW RESPONSES TO PROLONGED CONTROLLED HYPOTENSION IN THE DOG

Authors: JL Plewes, M.D., Ph.D. and LE Farhi, M.D.

Affiliation: Department of Anesthesiology, University of Oklahoma, Oklahoma City, OK 73190 and Department of Physiology, State University of New York at Buffalo, NY 14214

Introduction. Controlled hypotension produced with sodium nitroprusside (SNP) is used as an adjunct to anesthesia in a number of situations, primarily to decrease blood loss - the advantages including the improvement of the operative field and a decrease in the need for blood transfusion. Since some procedures may go on for long periods, we wanted to determine whether during 3 hours of controlled hypotension both cardio-respiratory stability and the distribution of peripheral blood flow are maintained.

Methods. Nine mongrel dogs (average wt. 20 Kg) were anesthetized with sodium pentothal, intubated, paralyzed with pancuronium, and maintained with 1.5% halothane in oxygen. Catheters were placed in a peripheral vein, the femoral artery, the left ventricle, and the pulmonary artery. After 2 hours of anesthesia, blood gases and peripheral and central pressures were measured. Cardiac output was determined (thermodilution), and an injection of radio-labelled 15 μ microspheres was made into the left ventricle to use for later analysis of the distribution of peripheral blood flow. Controlled hypotension to a mean pressure of 55 mmHg was then produced with an IV infusion of SNP. All variables were re-measured, and repeat microsphere injections were performed at 30, 60, 120, and 180 minutes after the start of hypotension. After this the animal was killed (IV KCl), and the organs removed and fixed in formalin. Radioactivity in tissue samples was determined and blood flows calculated by reference to the radioactivity in blood samples drawn at known rate from the aorta during the time of injection.(1)

Results. Mean arterial pressure was decreased from 86 mmHg to about 55 mmHg during the SNP infusion. There were no changes in cardiac output, heart rate, blood gases, or pH during the 180 minutes. Total peripheral resistance (TPR) decreased and remained significantly lower than control. (Table 1)

Table 1. Cardio-respiratory variables at control, and at times in minutes after onset of hypotension. Values are means. (*-p < 0.05 compared to control)

Variable	CON	30	60	120	180
Card. Out.(1/min)	2.77	2.69	2.72	2.95	3.10
Heart Rate (/min)	88	91	99	107	113
Art. press. (mmHg)	86	56*	55*	57*	58*
TPR (PRU)	0.027	0.018*	0.017*	0.017*	0.016*
PaO2 (mmHg)	578	576	577	577	575
PvO2 (mmHg)	69	68	73	77	78
PaCO2 (mmHg)	30	29	30	30	30
PvCO2 (mmHg)	35	36	38	37	38
pH	7.42	7.41	7.39	7.38	7.38

Blood flow increased to the brain, the increase going entirely to cortical grey areas and the central nuclei. Flows also increased to the liver, the pancreas, and the diaphragm. (Table 2) There were no changes in blood flows to retina, spinal cord, cecum, heart, renal cortex, or skeletal muscle. By 60 min, there were significant increases in blood flow to skeletal muscle and heart, and blood flow to liver had returned to control levels. By 120 min, there were significant decreases in blood flow to the renal cortex.

Table 2. Tissue blood flows (ml/gm/min) at control, and at times in minutes after onset of hypotension. Values are means. (*-p<0.05 compared to control)

TISSUE	CON	30	60	120	180
Brain	0.55	0.70	0.80*	0.80*	0.85*
Cort. White	0.64	0.68	0.70	0.66	0.69
Cort. Grey	0.74	1.15*	1.30*	1.23*	1.26*
Caudate	0.96	1.33	1.46*	1.58*	1.61*
Retina	2.5	2.8	2.6	2.6	2.5
Renal (outer)	6.33	6.80	6.28	4.96	4.30*
Renal (inner)	5.57	6.46	5.57	3.76*	2.90*
Spinal Cord	0.14	0.20	0.20	0.20	0.20
Heart	0.43	0.57	0.72*	0.92*	1.15*
Liver	0.22	0.37*	0.28	0.20	0.14
Pancreas	0.21	0.33*	0.39*	0.41*	0.33*
Duodenum	0.51	0.84	0.91*	0.87*	0.87*
Cecum	0.57	0.58	0.66	0.65	0.67
Triceps	0.037	0.044	0.066*	0.103*	0.150*
Masseter	0.032	0.036	0.054	0.079*	0.080*
Diaphragm	0.032	0.079*	0.14*	0.25*	0.30*

Discussion. Sodium nitroprusside produced a stable hypotension due entirely to a decrease in TPR. This was due for the first 30 min to a fall in resistance in beds such as brain, liver, and gut. By 60 min, gut resistances had begun to return to normal, but blood flow was increasing to skeletal muscle. The only organ in which significant decreases in blood flow were seen was the renal cortex (-22% after 120 min, -33% after 180 min). Over the 180 min there were no changes in blood gases or pH, and so this duration of controlled hypotension seems to produce no negative effects on respiratory function. With the exception of a relatively small decrease in renal cortical flow, it would appear that 3 hours of controlled hypotension produced with SNP, in association with halothane anesthesia, does not produce cardiorespiratory changes or changes in the distribution of peripheral blood flow that represent a danger.

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Title: INTRAOPERATIVE EVALUATION OF A WARMING VEST AND CAP DURING LOWER EXTREMITY ORTHOPEDIC PROCEDURES

Authors: TJ Radel, CRNA, MSN, MD Fallacaro, CRNA, MSN, TS Sievenpiper, MD, DA Whalen, Jr, MD.

Affiliation: Grad. Division, School of Nursing, and Dept. of Anesthesiology, School of Medicine, SUNYAB, Buffalo, NY and Anesthesiology Section, Veterans Administration Medical Center, Buffalo, NY

Introduction. Decreases in core body temperature can occur with general anesthesia (1). Methods of diminishing patient heat loss have been developed but are often not applicable to patients undergoing lower extremity procedures on fracture tables. We have evaluated a circulating-fluid warming device designed to be used with such patients and to be compatable with commonly available hyperthermia-hypothermia units.

Methods. This study was approved by the hospital committee on human studies and informed written consent was obtained from each subject. Thirty male patients scheduled for lower extremity orthopedic procedures were randomly assigned to one of three groups (n=10 for each). 1) Control - patients covered with two blankets. 2) Passive - as in group 1 with additional passive heat loss protection provided with two cotton shirts and a cotton cap. 3) Active - as in group 2 with the addition of a circulating-fluid vest and cap fashioned from material used in the construction of warming blankets currently available (Gaymar, Inc.). The vest and cap were connected to a Gaymar Medi-Therm heat exchange console with the circulating fluid at a temperature of 38 C. Premedication consisted of diazepam 0.1 mg/kg po and Atropine 0.4 mg IM one hour prior to surgery. All IV fluids and blood products were delivered at 37 C. All patients received general anesthesia with nitrous oxide, oxygen, and isoflurane. Procedures were of one hour duration or more (mean=135 min). Room temperatures were 20 C $\underline{+}1$. Temperature measurements were made using a YSI 43TA thermometer with YSI series 400 rectal probes and Gaymar DP400 single-use esophageal probes. First measurements were obtained within 5 minutes after induction of anesthesia and subsequent measurements taken every 15 minutes. End measurements were obtained just prior to moving the patient from the operating table. Results were analyzed using one-way analysis of variance (ANOVA), and planned comparisons between groups for control-passive and control-active group pairs were made using unpaired t-tests.

Results. No adverse effects related to the warming device were observed. Duration of anesthesia, age, weight, height, body surface area, and estimated blood loss for the three groups did not vary significantly (p>0.2). Tables I and II present group means for the first and last temperatures of the anesthetic period. Group means for the temperature change over the total period are also presented. For both esophageal and rectal temperatures there were no differences among the group means for the first temperature readings. Differences among means were statistically significant for the last temperatures and for the total temperature change. Using the planned comparison analysis the differences between active and control groups were found to be statistically significant (p<0.02 - rectal, p<0.01 - esoph.), while those between passive and control groups were not (p>0.25).

Figure 1 presents the esophageal temperatures from 0 to 120 minutes, after which time there were too few patients for meaningful comparison. As can be seen the difference between the active and control groups became statistically significant at 60 minutes and longer. There was no significant difference between the control and passive groups at any time. Results for the rectal temperatures were closely similar to the esophageal temperatures.

Discussion. During lower extremity orthopedic procedures core body temperature was maintained more effectively in patients wearing a newly designed warming vest and cap than with passive methods. Though this advantage appears slight under 60 minutes, significant differences were observed from 60 to 120 minutes.

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TABLE I
Esophageal Temperatures (deg C) - mean (SD)

GROUP	BEGIN ANESTH.	END ANESTH.	CHANGE TEMP
CONTROL	36.3 (0.8)	35.4 (0.7)	-0.9 (0.3)
PASSIVE	36.3 (0.7)	35.3 (0.7)	-1.1 (0.8)
ACTIVE	36.6 (0.6)	36.3 (0.6)**	-0.3 (0.4)**
ANOVA	p = 0.40	p < 0.01	p < 0.01

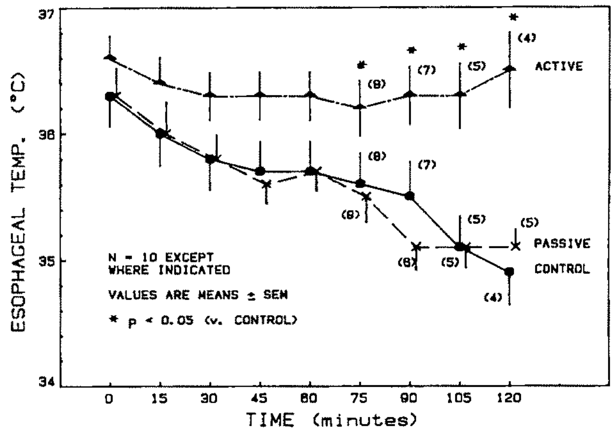
n = 10 each group ** p<0.01 t-test (v. control)

TABLE II
Rectal Temperatures (deg C) - mean (SD)

GROUP	BEGIN ANESTH.	END ANESTH.	CHANGE TEMP
CONTROL	36.4 (0.8)	35.5 (0.9)	-0.9 (0.4)
PASSIVE	36.6 (0.5)	35.5 (0.6)	-1.1 (0.6)
ACTIVE	36.8 (0.5)	36.4 (0.5)*	-0.4 (0.3)*
ANOVA	p = 0.37	p < 0.02	p < 0.02

n = 10 each group * p<0.02 t-test (v. control)

FIGURE 1



TITLE: MATERNAL AND NEONATAL EFFECTS OF EPIDURAL LIDOCAINE IN PREECLAMPTIC WOMEN UNDERGOING CESAREAN SECTION

AUTHORS: J. Ramanathan, M.D.*, M. Bottorff, Pharm.D.**, B.M. Sibai, M.D.***, Departments of Anesthesiology*, Clinical Pharmacy**, and Obstetrics and Gynecology***

AFFILIATION: University of Tennessee Center for the Health Sciences, 956 Court Ave., Box 21, Memphis, TN 38163

Introduction. Recent studies have shown that lidocaine is a safe local anesthetic both for the mother and the neonate when used for epidural anesthesia in normal healthy patients undergoing ceasarean section (c. section) (1). However, it is not clear what effect this drug would have in patients with moderate to severe preeclampsia with hypertension and central nervous system hyperirritability. This study was therefore undertaken to determine the maternal and neonatal effects of lidocaine in preeclamptics as compared to normal patients.

Methods. This study was approved by the Institutional Review Board and informed consent obtained from each patient. Two groups of patients were studied. Group I consisted of five normal healthy women without any medical complications undergoing c.sections. Group II consisted of ten patients with moderate to severe preeclampsia with hypertension, proteinuria, edema and exaggerated tendon reflexes. All patients in this group were receiving continuous infusion of magnesium sulfate, 2 gm/hr and their coagulation profile was normal. The central venous pressure (CVP) was monitored in this group and was maintained in the range of 6 - 8 cms H_2O. Epidural anesthesia was established in the usual manner using 2% lidocaine 18 - 20 mls. Samples of blood were drawn for lidocaine levels from an indwelling venous catheter at 3, 5, 10, 15, 20, 30, 45 and 60 minute intervals and then at 1.5 hr, 2, 4, and 6 hrs. All samples were placed in ice, centrifuged and frozen at -20°C until analysis. At the time of delivery the Apgar Scores were noted and samples of blood were drawn from umbilical artery and vein for acid base status and lidocaine levels. The Early Neonatal Neuro-behavior Scores (ENNS) were evaluated at 2 hrs and 24 hrs after birth. The statistical analysis was performed using Student's t-test for unpaired data and a P-value less than 0.05 was considered significant.

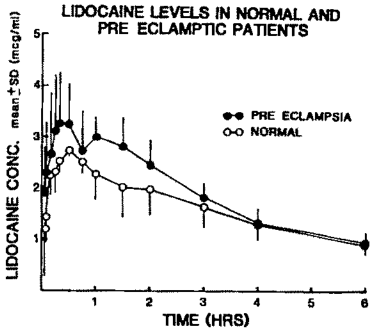
Results. The two groups were similar in age, height, weight, parity and gestational age. There were no significant differences in the total dose of lidocaine, the peak plasma concentration (cp), the time to reach the peak concentration (Tmax) and the umbilical vein/maternal vein ratio. (Table 1, Fig.1). The calculated area under the concentration time-curve was significantly higher ($P < 0.02$) and the total body clearance significantly slower ($P < 0.05$) in Group II. All other variables including the Apgar Scores, acid-base status and ENNS were not significantly different between groups.

Discussion. In patients with preeclampsia, in addition to hypertension and proteinuria there is hepatic derangement and increased volume of distribution (2, 3). They also have central nervous system hyperirritability with lower seizure threshold and imminent convulsions. Lidocaine is almost entirely metabolized in the liver. Our study shows that although the peak plasma levels are not significantly different from normals, the total body clearance is prolonged in preeclampsia probably due to altered hepatic metabolism. This finding may become significant if repeated doses of lidocaine are used, since higher levels of the drug might be potentially toxic in these patients with lower seizure threshold.

Table 1.

	P	Group 1	Group II
Dose of lidocaine (mgms)	NS	370 ± 20	372 ± 27
Peak plasma lidocaine concentration(mcg/ml)	NS	2.8 ± 0.2	3.4 ± 0.8
Time to reach peak plasma concentration (minutes)	NS	34 ± 13	37 ± 13
Area under the conc-time curve (mcg-hr/ml)	0.20	14.1 ± 1.3	18.5 ± 4.7
Total body clearance (L/hr)	0.05	31.1 ± 4.4	24.5 ± 7.1
Umbilical vein/maternal vein ratio	NS	0.71 ± 0.13	0.57 ± 0.18

Figure 1.



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TITLE: ETOMIDATE AND ADRENOCORTICAL SUPPRESSION

AUTHORS: RR Raval, M.D., FC Fan, M.D.*, E Samojlik, Ph.D.

AFFILIATION: Departments of Anesthesiology* and Endocrinology, Newark Beth Israel
Medical Center University of Medicine and Dentistry-New Jersey Medical School

Introduction. Etomidate is a new non-barbiturate intravenous anesthetic agent with several advantages over thiopental, including short duration of action, less cardiorespiratory depression and less histamine release. However, recent reports suggest that etomidate can induce adrenocortical suppression after short term or long term use (1, 2, 3). As a result of these findings, it has been suggested that the drug no longer be used for sedation or for anesthesia (1). However, the evidence of a single dose of etomidate used for induction of anesthesia causing cortisol suppression is lacking; therefore, we evaluated the effect of single induction dose of etomidate as compared to thiopental on the suppression of cortisol secretion.

Methods. Fifty randomly selected patients were studied. All the patients were premedicated with meperidine and hydroxyzine. Control samples were drawn prior to induction of anesthesia, this was followed by an injection of 150 µg of fentanyl. Anesthesia was induced with etomidate 0.3 mg per kilogram (n = 33) or thiopental 4 mg per kilogram (n = 17). Blood samples were drawn at intervals of 3, 10, 30 and 60 minutes post injection for analysis of serum cortisol levels. In a sub-group of etomidate patients (n = 14), additional blood samples were drawn at 120 and 180 minutes. The blood pressure and pulse rate were also monitored throughout the period of study. Results were analyzed by the use of student's paired T test.

Results. All surgical patients had normal serum cortisol levels before surgery (15.1 ± 4.6 µg/dl). After induction of anesthesia, both thiopental and etomidate depressed serum cortisol levels to 30 percent of control. Serum cortisol levels in thiopental group returned to control at 60 minutes while in etomidate sub-group serum cortisol levels were significantly lower ($p < 0.01$) than control value at 120 and 180 minutes. The blood pressure and pulse rate remained unchanged throughout the period of study.

Discussion. Since the infusion of fentanyl also cause transient depression of serum cortisol secretion (4), the depression of serum cortisol level immediately following the injection is probably a reflection of the onset of a stress-free anesthetic status induced by these anesthetics. This is evidenced by the rapid recovery of serum cortisol level with thiopental (Fig 1), where the stress level may have heightened with the onset of surgery. The longer depression of cortisol secretion (> 3 hours) by etomidate could be a result of direct depression of the hormone synthesis. Wagner et al. (3) has shown that etomidate blocks adrenal steroid synthesis by inhibiting cholesterol-side-chain cleavage enzyme and 11 Beta-hydroxylase in the rat adrenal cell preparations due to the imidazole structure in the etomidate compound. As a result, there is an increase of serum 11-Deoxycortisol secretion. In a preliminary study, we have also demonstrated an increase of serum 11-Deoxycortisol level in the etomidate patients. The longer depression of serum cortisol level in these patients does not associate with any recognizable hemodynamical changes. Although the depression of cortisol secretion in the etomidate patients is not sufficient to cause hemodynamical changes, one should be aware of this potential problem when using etomidate to induce anesthesia.

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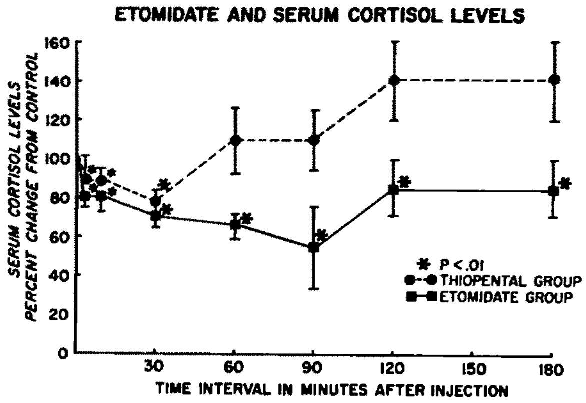

Fig. 1

Title: INFLUENCE OF I.V. NALOXONE INFUSION ON ANALGESIA AND UNTOWARD EFFECTS OF EPIDURAL MORPHINE

Authors: N Rawal, M.D., Ph.D., U Schött, M.D., B Tandon M.D.,* U Sjöstrand, M.D., Ph.D., and M Wennhager
Affiliation: Departments of Anesthesiology and Intensive Care, Örebro Medical Center Hospital, Örebro, and
Central Hospital, Karlskoga*, Sweden

Introduction. Controlled studies have shown that postoperative analgesia by opiates injected epidurally is superior to other alternatives (1). However, the widespread use of this technique is restricted by the requirement of strict postoperative surveillance due to the risk of delayed respiratory depression. Respiratory depression and adverse effects such as urinary retention, nausea/vomiting, pruritis can be treated by naloxone (2). It is unclear if epidural morphine analgesia is also reversed by naloxone. The present double blind study was undertaken to compare the influence of two different concentrations of continuous i.v. naloxone infusion on the analgesia and adverse effects of epidural morphine.

Method. Fortyfive ASA class I or II patients undergoing elective gall bladder surgery participated in the study which was approved by the Local Ethics Committee. Informed consent was obtained. The patients were operated under epidural block combined with light endotracheal anesthesia. Postoperatively the patients were nursed at the Intensive Care Unit (ICU) for 24 hours, during this period ECG was monitored continuously and pulse, blood pressure and respiratory frequency registered every 15 minutes. Samples were analysed for arterial blood gases every 2 hours for 24 h. Postsurgical analgesia was provided on demand by 4 mg morphine injected in the epidural catheter. The patients were randomly divided into 3 groups of 15 each and naloxone infusion was given in a double blind fashion. Patients in group A received a bolus injection of 0.4 mg i.v. naloxone followed by an i.v. infusion at the rate of 10 µg/kg/h. Patients in group B were given half the dose i.e. 0.2 mg bolus injection followed by infusion of 5 µg/kg/h of naloxone. Patients in group C received saline as bolus injection and as infusion. Pain relief was assessed by Visual Analog Score (VAS) every hour for 24 h. Urinary retention was defined as inability to micturate spontaneously within 6 h of surgery.

Results. Low VAS scores (below 3) indicated effective analgesia in all patients. However, the amount of morphine required for pain relief was significantly larger in group A as compared to the other groups. Table shows the duration of analgesia and the total dose of morphine required. The mean respiratory frequency during the 24 h postoperative period was generally lower in the placebo group. Three patients (20%) in the placebo group had respiratory frequencies of 10 or below on different occasions during the 24 h postoperative period. This was not seen in any of the patients receiving naloxone. As compared to the placebo group respiratory frequency was significantly higher from 9-17 h in group A ($p<0.05$) and at 6, 9, 10 and 14 h in group B ($p<0.05$). A similar tendency was seen in $PaCO_2$ changes. Compared to preoperative values postoperative $PaCO_2$ was lower in patients receiving naloxone, the changes were significant from 2-14 h in group A ($p<0.05$) and from 2-10 h in group B ($p<0.05$).

Discussion. Our findings indicate that naloxone has a dose related effect on epidural morphine analgesia. A minimal decrease in the duration of analgesia was noted in patients receiving 5 µg/kg/h naloxone, however, 10 µg/kg/h doses naloxone reduced the duration of analgesia by about 25%. A tendency towards respiratory depression following injection of 4 mg morphine epidurally could be reversed by naloxone infusion. Although both concentrations of naloxone were adequate for this purpose, the effects were dose dependent. Also, naloxone reduces the risk of adverse effects. Dilute infusion of naloxone can therefore be advocated in patients with high risk of developing postoperative pulmonary complications who would otherwise be deprived of a superior form of analgesia due to lack of ICU facilities.

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Table. Influence of naloxone on analgesia and adverse effects of epidural morphine.

	Group A (n=15) Naloxone 10 µg/kg/h	Group B (n=15) Naloxone 5 µg/kg/h	Group C (n=15) Saline
Duration of analgesia *(h)	13.7±2.3	17.8±3.5	18.5±3.4
Total dose of epidural morphine * (mg)	9.6±1.2^x	6.4±0.7	5.9±0.5
Pulmonary complications **	1 (7%)	1 (7%)	3 (20%)
Urinary retention **	5 (33%)	8 (53%)	10 (67%)
Nausea/ vomiting **	1 (7%)	2 (13%)	3 (20%)
Pruritis **	-	1 (7%)	1 (7%)

*Values are means ± SEM. **Number of patients
^{x}p<0.01 vs placebo values

Title: GAS FLOWS WITH A COAXIAL CIRCUIT AT 1.3 AND 2.3 MAC HALOTHANE IN SPONTANEOUSLY BREATHING CHILDREN

Author: R.L. Rayburn, M.D.

Affiliation: Department of Anesthesia, Primary Children's Medical Center and University of Utah
Medical Center, Salt Lake City, Utah 84103

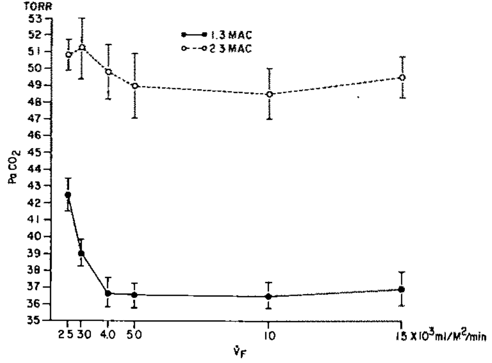
Introduction. Development of the coaxial circuit renewed interest in the characteristics of Mapleson D type systems during spontaneous respiration. When rebreathing is disregarded in favor of maintaining normal arterial CO_2 tensions ($PaCO_2$), recommended fresh gas flows ($\dot{V}_F$) in adults have ranged from 100-300 ml/kg/min(1,2). In adults a more respiratory depressant anesthetic, enflurane, causes a greater initial volume of CO_2 rebreathing at high $\dot{V}_F$ with a lesser increase in CO_2 rebreathing as $\dot{V}_F$ are decreased when compared to halothane (3). However, no study has addressed the $\dot{V}_F$ necessary to prevent an increase in $PaCO_2$ in spontaneously breathing children at different depths (respiratory depression) of halothane. This study was designed to determine if a spontaneous respiration $\dot{V}_F$ index which would prevent a rise in $PaCO_2$ from control could be determined for various depths of halothane anesthesia.

Methods. Two groups of children having urologic or extremity surgery lasting more than 2 hours were studied. Each child's parents gave informed consent and the study was approved by the hospital's Human Research Committee. Group 1 consisted of 16 unpremedicated children (age 1.5 - 11 years) anesthetized with N_2O/O_2 (50%-50%) and halothane using a coaxial circuit. All patients were intubated and 9 received a caudal while 7 had no regional anesthesia. $\dot{V}_F$ was then statistically set randomly at: 15,000, 10,000, 5,000, 4,000, 3,000, or 2,500 ml/m^2/min, and the anesthetic set at 1.3 MAC (end tidal corrected for altitude) using a Beckman LB-2 halothane analyzer. Then a 22 or 24 gauge catheter was placed in the radial artery of the non-dominant hand. After 20 min of spontaneous respiration at a particular $\dot{V}_F$; heart rate (HR), blood pressure (BP), respiratory rate (f), esophageal temperature (ET), $F_{ET}CO_2$, F_ICO_2, PaO_2, $PaCO_2$, arterial pH, and tidal volume (TV) were measured. The $\dot{V}_F$ was then set at another flow keeping $F_{ET}H$ with N_2O at 1.3 MAC. Following each 20 min period, the above measurements were repeated. Group 2 consisted of 17 unpremedicated children (age 1.3 - 15 years). Eight had a caudal and 9 had no regional anesthesia. These children were treated exactly as Group 1 except $F_{ET}H$ with N_2O was kept at 2.3 MAC.

Results. HR, BP, f, ET, PaO_2, and arterial pH showed no significant difference at any $\dot{V}F$ when compared with control values obtained at $\dot{V}F$ 15,000 ml/m^2/min. In group 1 (seventy-seven sets of determinations) $PaCO_2$ did not increase significantly from the control of 36.8 torr until $\dot{V}_F$ was below 4000 ml/m^2/min. (Fig. 1) $F_{ET}CO_2$ and TV also only increased when $\dot{V}_F$ was less than 4000 ml/m^2/min. In group 2 (eighty-eight sets of determinations) $PaCO_2$ did not show a significant increase from the control of 49.5 torr at any $\dot{V}_F$ tested. (Fig. 1) TV also showed no increase at any $\dot{V}_F$. $F_{ET}CO_2$ did show a significant rise when $\dot{V}_F$ was less than 4000 ml/m^2/min. In both groups, F_ICO_2 varied inversely with $\dot{V}_F$, but was only significant at 5000 ml/m^2/min or less. Surgical stimulation was not influencial since there was no significant difference between patients receiving and those not receiving regional anesthesia in either group.

Discussion. In this study a rise in $PaCO_2$ was used as the indicator of significant CO_2 retention under light and deep halothane anesthesia. At 1.3 MAC (light) halothane anesthesia significant CO_2 retention occurred at $\dot{V}_F$ less than 4000 ml/m^2/min. These results are similar to those reported for adults with halothane anesthesia (3). At 2.3 MAC (deep) halothane anesthesia no significant CO_2 retention greater than the control was seen at any $\dot{V}_F$ tested. This is similar to results with enflurane (3), and suggests that the initial rise in $PaCO_2$ produced by the respiratory depression of the anesthetic is not further elevated with the $\dot{V}_F$ used in this study. Thus, this study indicates that the $\dot{V}_F$ in a coaxial circuit during spontaneous respiration in children at the usual clinical depths of halothane/N_20 anesthesia should probably not be less than, nor need exceed, 4000 ml/m^2/min to prevent significant CO_2 retention.

FIG. 1



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Title: COMPARISON OF PSYCHOMOTOR SKILLS AND AMNESIA AFTER INDUCTION OF ANESTHESIA BY MIDAZOLAM OR THIOPENTAL

Authors: JA Reitan, M.D.,[*] RW Porter, M.D.,[**] and M Braunstein, M.S.[*]

Affiliation: Department of Anesthesiology,[*] University of California School of Medicine, Davis, California, and the Department of Anesthesiology,[**] Brackenridge Hospital, Austin, Texas

Introduction. Midazolam maleate is a water soluble benzodiazepine with a shorter half life and duration of action than diazepam. It has been shown to have a relatively rapid onset (1) and, as such, has been suggested as an anesthetic inducting agent for short procedures (2). The purpose of our study was to ascertain the rapidity of return of psychomotor skills with midazolam compared to thiopental and to assess the drug's short-term amnestic qualities.

Methods. Sixty-two ASA I and II patients undergoing minor elective surgery were included in the double-blind, randomized, parallel-group study. On the day of surgery, prior to anesthesia, all subjects (31 midazolam, 31 thiopental) were treated for hand coordination (peg board manipulation), vigilance (serial dot crossing), spatial concepts (placing blocks in holes), and short-term learning (repeated digit series). Additionally, they were shown a large dollar bill for post-anesthesia recognition (retrograde amnesia).

Five minutes prior to induction of anesthesia all subjects received fentanyl 2.0 μg/kg IV. Anesthesia was induced with either midazolam (0.2 mg/kg) or thiopental (3.5 mg/kg) and induction was considered complete with the absence of eyelid reflex, voluntary movement, and response to verbal command. Standard cardiovascular and respiratory variables were monitored periodically throughout anesthesia. Surgical anesthesia included 67% N_2O and increments of fentanyl (25 μg) or the study drug (25% of inducting dose) given appropriately to attenuate responses to surgical stimuli.

When they were judged non-drowsy (normally conversant and oriented X 3) in the recovery room, all subjects were shown and identified pictures of 10 common objects and the psychomotor tests were repeated hourly for 6 hours and again 24 hours after orientation. At 24 hours the object pictures and large dollar bill were displayed again and the patients were asked to identify those seen before. Recognition constituted lack of amnesia. Statistical analysis between groups was by analysis of variance for anesthetic induction time and time to orientation. Recovery of psychomotor skills was judged by the Cox proportional regression model and amnesia was compared by the Mantel-Haensgel test. Values denote the mean ± 1 SEM unless otherwise noted. This investigation was approved by the Human Research Committee.

Results. Both groups were similar with respect to age, weight, length of surgery and drug increments during surgery. However, there were statistically significant differences between the midazolam and thiopental groups for anesthetic induction time (97 ± 10.9 vs 59.4 ± 5.0 sec - $p<0.01$ and time to orientation (31.7 ± 4.2 vs 11.0 ± 1.1 min - $p<0.01$). Psychomotor skills returned more slowly with midazolam (Table 1) and anterograde amnesia was noted in 85% of the midazolam patients compared to 31% in the thiopental patients (Table 2). Retrograde amnesia was not demonstrated in either group. There were no significant differences between the drug groups in postoperative complaints.

Discussion. While return of psychomotor skills was more prolonged with midazolam, it was lengthy in both groups and supports the suggestion that, following minor surgery under general anesthesia, patients have a much delayed return of motor and judgmental skills (3). The longer induction time and interval to postoperative orientation for the benzodiazepine are within acceptable ranges for short surgical procedures. Overall, patient acceptance of both drugs was equivalent and the degree of anterograde amnesia was acknowledged positively by the affected midazolam patients.

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Table 1

PSYCHOMOTOR SKILL TESTS

Time For 75% of Patients To Reach Baseline Levels

	MIDAZOLAM (Min)	THIOPENTAL (Min)
PEGS TURNED IN 30 SECONDS	320	250*
DOTS CROSSED CORRECTLY	281	194**
BLOCKS INSERTED	241	151
DIGITS REPEATED CORRECTLY	114	48**
DROWSINESS	122	43**

*Thiopental Shorter Than Midazolam Group ($p<0.05$)
**Thiopental Shorter Than Midazolam Group ($p<0.01$)

Table 2

ANTEROGRADE AMNESIA (% Of Patients Evaluated)

	ABSENT	PARTIAL	COMPLETE
MIDAZOLAM	0	15.2	84.8*
THIOPENTAL	51.4	17.1	31.4

*Differs from Thiopental Group ($p<0.01$)

Title: GLUCOSE METABOLISM IN THE MOTHER AND FETUS DURING CESAREAN SECTION UNDER EPIDURAL ANESTHESIA

Authors: I. Rock, M.D., R. Sheth, M.D., S. Ramanathan, M.D., J. Arismendy, B.S., H. Turndorf, M.D.

Affiliation: Department of Anesthesiology, New York University Medical Center,
550 First Avenue, New York, N.Y. 10016

Introduction: Animal fetuses utilize only 50% of their total O_2 consumption for aerobic metabolism of glucose (G) and the balance for metabolizing other substrates, notably lactate (L).[1,2] This study assesses in humans how the aerobic requirements are met in maternal and fetal tissues.

Methods: The study was approved by the local research committee. Patients gave informed consent. Twenty healthy patients (age, 28±3, 1 SD and weight 73±4 kg) carrying a single term gestation were scheduled for elective cesarean section under lumbar epidural anesthesia (LEA). They were hydrated with 1200 ml lactated Ringer's solution before LEA was induced by injecting 18±5 ml lidocaine 1.5% with 1:200,000 epinephrine through a catheter inserted through the L3-L4 intervertebral space. Patients inhaled 0.5 FIO_2. Systolic blood pressure was maintained at or above 100 torr by 5 mg intravenous ephedrine injections. Left uterine displacement was maintained. Maternal metabolism was studied in the forearm. At the time of delivery, blood samples were obtained from the maternal radial artery (MA) and the median basilic vein (MA and MV) for the measurement of PO_2, PCO_2, pH, hemoglobin (Hb) concentration (%), and Hb oxygen content ($CHbO_2$), glucose, lactate and pyruvate (P). Neonatal umbilical vein and arterial (UV and UA) blood was sampled for the same measurements. Uterine incision to delivery (UD) interval and neonatal Apgar scores were noted. An Instrumentation Lab (IL) co-oximeter 282 was used to measure Hb% and $CHbO_2$. This instrument is accurate for these measurements.[3] Gregory's values for adult and fetal Hb-O_2 carrying capacity was used to program the co-oximeter.[4] Total blood O_2 content (CBO_2) was calculated by adding the volume of oxygen in physical solution (0.0031 x temp corrected PO_2) to HbO_2. An IL 1303 blood gas analyzer was used to measure pH and gas tensions. G (glucose oxidase method), L and P (Lactic dehydrogenase method) were measured in deproteinized whole blood. Base excess (BE) was calculated by Severinghaus' equation. Excess lactate (XL, the portion of the measured L which cannot be accounted for by the measured P) was calculated using Huckabee's equation. XL represents anaerobic metabolism. Results were expressed as $\bar{X}$ ± SEM and analyzed by t-test.

Results: UD interval was 110 ± 8 seconds. No baby had an Apgar score of <7 at 1 min or <9 at 5 min. Seven patients required 11 ± 1 mg ephedrine. Maternal and fetal pH, blood gas tensions and BE are shown in Table 1. The maternal A-V G difference (Δ) was 0.86 mmol/L and the CBO_2 was 2.99 mmol/L. (Table 2.) The figures for the neonate were 0.78 for ΔG and 2.79 for ΔCBO_2. The MV L was 0.29 mmol (ΔL) higher than MA L ($p<0.01$) and UA L 0.03 mmol higher than UV L ($p<0.05$). P did not differ between MA and MV or UV and UA. XL was significantly greater in MV blood than MA but did not significantly differ between UV and UA(table 2).

Discussion: Six moles of O_2 are required for complete aerobic G combustion. Thus, the observed ΔCBO_2 in the mother and fetus could account for the aerobic metabolism of 0.50 mmols of G in the mother and 0.465 mmol in the fetus. Higher L levels in MV and UA without P increases suggest some anaerobiasis. One mole of G yields 2 moles of L anaerobically. The maternal ΔL may account for the anaerobic metabolism of 0.145 moles of G and fetal ΔL for only 0.06 moles of G, thus explaining the higher XL in MV blood than in UA blood ($p<0.01$). Uteroplacental perfusion and oxygenation were well maintained which obviated the need for anaerobic metabolism in the mother and fetus. The low level anaerobiasis probably represents the same mechanism which becomes prominent during hypoxia.[5] The remaining 0.215 mole of G (0.86-(0.50+0.145)) was probably stored as glycogen in the mother. In the fetus, the balance 0.26 moles (0.78-(0.465+0.06)) was stored. Because UA L was greater than UV L, the fetus probably did not utilize L as a nutrient. The fate of G in the mother and fetus is summarized in the figure. In summary, all aerobic demands are met by G in human fetuses, which explains why neonates tolerate hypoglycemia poorly.

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Table 1:

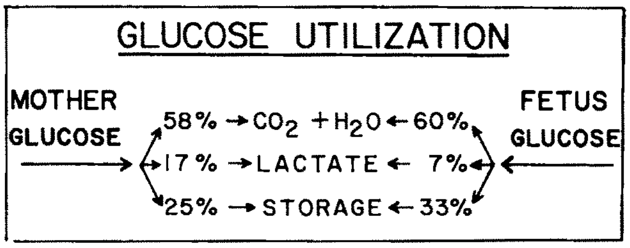
	MA	MV		UV	UA
PO_2(torr)	210 (10)	29 (3)		34 (2)	17 (2)
PCO_2 (torr)	30	41	(1)	41	50
pH	7.41	7.32	(0.01)	7.33	7.28
BE (mmol/l)	-6.2	-6.6	(0.7)	-3.85	-3.31

Table 2:

(mmol/L)	MA	MV		UV	UA
G	6.16	5.3	(0.3)	5.18	4.4
L	1.08	1.37	(0.1)	0.97	1.1
P	0.08	0.08	(0.01)	0.07	0.08
XL	0.21	0.59	(0.01)	0.22	0.29
CBO_2 (STPD)	5.66	2.67	(0.2)	4.97	2.18

Legend: Figures within parentheses are ± 1 SE

Figure:



Title: EFFECT OF NITROUS OXIDE ON IN VITRO FERTILIZATION SUCCESS RATE

Authors: M. F. Roizen, M.D., P. V. Dandekar, M.D., M. K. Cahalan, M.D., R. Cronnelly, M.D., Ph.D.,
P. A. Dailey, M.D., L. Litt, M.D., Ph.D., E. I. Eger II, M.D., M. A. Rosen, M.D.,
Y. J. Sohn, M.D., R. H. Glass, M.D., N. L. MacKenzie, B.A.

Affiliation: Department of Anesthesia, University of California, San Francisco, California 94143

Introduction. Since N_2O interferes with DNA synthesis (1), it may be detrimental to early embryonic development. Such an effect may be a cause of the wide variation in success rate of egg fertilization and pregnancy following in vitro fertilization (IVF) (2). We investigated whether N_2O influences the success rate of fertilization or pregnancy after IVF.

Methods. We obtained institutional approval and informed consent to study patients undergoing elective oocyte retrieval for IVF. Thirty-two patients were randomly assigned to receive an anesthetic with (n = 17) or without (n = 15) 60% N_2O. All patients received < 1.15 MAC of inhalation anesthetic (N_2O plus isoflurane). Anesthesia was induced with thiopental, and endotracheal intubation was facilitated by a small dose of d-tubocurarine and succinylcholine 1.5 mg/kg. Subsequent muscle relaxation was provided by isoflurane and, if needed, an infusion of succinylcholine. In addition, 19 of the 32 randomized subjects received fentanyl (less than 4 ug/kg) prior to oocyte retrieval (not different between groups). Ventilation was controlled to obtain end-tidal concentration of 30-35 mmHg for carbon dioxide, and less than 1.15 MAC for isoflurane and N_2O (as monitored by mass spectroscopy). In all instances, the gas insufflated into the peritoneum was carbon dioxide. The number of oocytes retrieved, their fertilization rate, and the number of resulting pregnancies were compared using Chi square analysis with a Yates correction.

Results. Forty-six oocytes were obtained and 74% were fertilized for the 15 patients not given N_2O compared with 49 oocytes obtained and 73% fertilized for the 17 patients given N_2O ($P > 0.95$). Not enough pregnancies resulted to make statistical testing valid. For the total in vitro fertilization population (both randomized and not randomized), 61 oocytes were obtained and 75% were fertilized for the 21 patients not given N_2O, and 109 oocytes were obtained and 70% were fertilized for the 36 patients given N_2O ($P > 0.90$).

Discussion. Success rate of IVF might be as low as published for several reasons (2). Fertilization may be that low in vivo, the in vitro environmental conditions may not be perfect, or drugs administered during the procedures may alter oocyte fertilization. Anesthetic agents will be distributed to the follicular fluid and oocyte. Nitrous oxide might be expected to affect oocyte function and embryologic development by inhibiting methionine synthetase activity. It may thus decrease thymidine available for incorporation into DNA. However, because it can be diffused rapidly, nitrous oxide might not influence the success rate. Thus, in the few minutes it takes to transfer the oocyte to a test tube, virtually all nitrous oxide is gone from the oocyte milieu. Use of nitrous oxide might increase fertilization success by allowing reduced concentrations of other potentially toxic and less diffusible anesthetics. In fact, isoflurane has been reported to be teratogenic in one mice species. Human embryogenesis is most vulnerable to teratogenic trauma from days 18 to 60 of pregnancy. Theoretically, the effects of earlier exposure to toxins would be limited to developmental arrest, embryonic death, or failure to implant. In fact, over 350 babies have been born without a reported chromosomal abnormality after IVF. Thus, the concerns of anesthesia for the fetus during IVF can be directed toward maternal health and oocyte function.

Based on this limited data, nitrous oxide does not appear to affect fertilization of retrieved oocytes. Based on sample size, we would have found (with a 90% confidence) an effect of N_2O if it had caused as little as a 25% change in fertilization rate. This study will continue so that it can be determined if nitrous oxide has a small effect (25% or less) or affects the pregnancy rate of IVF. Further study contrasting spinal anesthesia with general anesthesia for IVF seems warranted.

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Title: AGING INCREASES HEMODYNAMIC RESPONSES TO INDUCTION AND INCISION

Authors: M. F. Roizen, M.D., G.H. Lampe, M.D., L.B. Sheiner, M.D., R.A. Alpert, M.D., B.M. Frazer, M.D., R.P. Chan, E.I. Eger II, M.D.

Affiliation: Departments of Anesthesia, Laboratory Medicine, Medicine, and Pharmacology, University of California, San Francisco, California 94143

Introduction. Clinical observation suggests that older individuals have more labile cardiovascular responses to anesthesia (depression) and surgery (stimulation).[1,2] To test this impression, we studied the hemodynamic and catecholaminergic responses to anesthetic induction and to incision.

Methods. With approval from our committee on human research and with informed consent, we randomly assigned 41 unpremedicated ASA I or II patients (aged 19 to 75) to receive 1.25, 1.5, or 1.75 MAC islflurane plus N_2O (combined MAC for isoflurane and N_2O) together with fentanyl 5 ug/kg and oxygen. Doses of isoflurane and fentanyl were age-adjusted according to previously published data for isoflurane.[3] Incision was made at least 20 min after induction of anesthesia with thiopental 4 mg/kg (age-adjusted) and endotracheal intubation (facilitated with succinylcholine). The dose of thiopental was also age-adjusted.[3] The fentanyl was given as a bolus at the time of intubation. Three and 1 min before induction and every 2 min following endotracheal intubation, we measured blood pressure and heart rate. Any time systolic blood pressure decreased to less than 80 mmHg in the "postinduction period" (i.e., after induction and before incision) hypotension was said to occur. Three and 1 min before incision and 3, 5, and 10 min ater incision, we measured systolic blood pressure and heart rate and obtained peripheral venous blood samples for measurement of norepinephrine and blood gases. Statistical analysis included least mean-squares regression and one- and two-way analyses of variance.

Results. Sixteen patients had systolic blood pressures less than 80 mmHg during the postinduction period: this hypotension occurred in 5 of 23 (22%) individuals under 41 years of age, in 7 of 14 (50%) between 41 to 66 years of age, and in 4 of 7 (57%) individuals age 66 or over ($p < 0.05$). The lowest systolic blood pressure (SBP) attained in the postinduction period correlated significantly with age for the entire group and in each MAC group. The correlation is defined by the line: $SBP = 110 - (0.46 \times age)$; ($r = 0.5$, $p < 0.007$). At any dose of anesthetic, older individuals had greater absolute and percentage increases in systolic blood pressure in response to incision. For example, at 1.25 MAC, the percentage change in blood pressure to incision $= (2 \times age) - 64$; ($r = 0.8$, $p < 0.02$, $n = 8$); and change in blood pressure $= (1.4 \times page) - 40$; ($r = 0.77$, $p < 0.03$). The increase in norepinephrine levels in response to incision tended to increase with age but did not reach statistical significance (e.g. $r = 0.44$, $p = 0.2$, $n = 6$, for 1.25 MAC).

Discussion. Our data support the clinical impression that postinduction hypotension is more likely to occur in the aged, and that incision is likely to produce a larger percentage increase in blood pressure in the aged. The large fraction of older patients who became hypotensive probably overestimates what happens in clinical practice: our protocol involved administering anesthesia for a substantial period of time without surgical stimulation. This time period existed to allow establishment of stable levels of anesthesia. Undoubtedly, in routine clincial practice, one tries to decrease the anesthetic administered when surgical stimulation is absent.

Aging may have produced greater changes in blood pressure in the postinduction period and after incision because elderly individuals tend to have cardiovascular compromise and operative procedures for diseases that produce dehydration. However, all our patients appeared to be normovolemic and all were ASA physical status class I or II. The larger percentage and absolute changes in blood pressure with induction and incision in the elderly also might be attributed to their less elastic arterial walls, to less efficient baroreceptors, to a greater change in alpha- versus beta- adrenergic responses to stimuli, or to a larger hormonal response in general to stimuli.[4] Perhaps the slope of the curve relating dose of anesthesia necessary to block movement to age is less steep than that relating dose of anesthesia necessary to block cardiovascular responses to age. This latter hypothesis remains to be proven.

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Title: ANAPHYLACTOID REACTIONS TO VASCULAR GRAFT MATERIAL

Authors: M. F. Roizen, M.D., G.M. Rodgers, M.D., Ph.D., F.H. Valone, M.D., G.H. Lampe, M.D., D.J. Benefiel, M.D., J.S. Smith, M.D., K.P. Cherry, M.D., J. Rapp, M.D., M. Oto, R.N., E.J. Goetzl, M.D.

Affiliation: Departments of Anesthesia, Medicine, Pharmacology, and Surgery, University of California, San Francisco, California 94143

Introduction. Persistent abnormal decreases in systemic vascular resistance (SVR) subsequent to restoration of flow after aortic reconstruction grafting is usually due to occult bleeding. When these decreases in SVR are followed by overt bleeding, an anaphylactoid reaction to graft material with release of chemical mediators of hypersensitivity is rarely suspected. In fact, no report of an anaphylactoid reaction to vascular grafting material exists in the literature. We present five cases of suspected anaphylactoid reactions to two vascular grafting materials; these reactions presented as rapidly decreasing SVR followed by consumption coagulopathy. In two of these cases, blood samples diverted from studies fortuitously in progress permitted biochemical verification of anaphylactoid reactions. Such biochemical markers were not present in control patients.

CASE REPORTS. Case 1: A 55-year-old female underwent aortoceliac and aorto-superior mesenteric revascularization on 6/28/81. Surgery proceeded uneventfully until the bifurcation graft (knitted Dacron-Milliknit 10 X 5 Lot 12B - preclotted) was opened. SVR (dynes•s•cm^{-5}) decreased from 1,800 to 833 over 10 min without evidence of bleeding. Ten min later, the graft began to leak rapidly from its interstices. Bleeding continued for 3 h. Analysis of plasma confirmed consumption coagulopathy. The graft was replaced by a different graft material 3 h later, but not before the patient received 76 units of blood. No biochemical evidence of a transfusion reaction was present. The patient died 8 days later of complications of consumption coagulopathy. Case 2: On 12/21/83 GAC underwent aortic reconstruction. Operation proceeded uneventfully until blood flow through the knitted Dacron graft (Milliknit 12 X 6 lot K8B - preclotted) was restored. SVR (dynes•s•cm^{-5}) fell from 1,800 (before declamping) to 860 3 min after flow was restored. Seven minutes later SVR uncharacteristically continuted to decline to 611. No surgical bleeding was found. No biochemical evidence of a transfusion reaction was present. The patient had cutaneous erythema. Ten minutes later, bleeding occurred through the interstices of the graft. SVR was restored 3 h later (12 units of blood had been transfused) only after replacing the graft with one made of another material. Case 3: On 12/22/83 a 70-year-old woman underwent aortic reconstruction, which proceeded uneventfully until the bifurcation graft (Milliknit 12 X 6 lot K8B - preclotted) was opened. SVR (dynes•s•cm^{-5}) dropped from 1,824 to 1,200 3 min after flow was restored and uncharacteristically to 580 over 20 min. In addition, cutaneous erythema occurred, and the graft started bleeding from its interstices. A 20-unit blood loss ensued over the next 30 min. With the previous day's experience (Case 2) in mind, consumption coagulopathy secondary to an abnormal reaction to the graft material was suspected. Evidence documenting consumption coagulopathy was obtained. No biochemical evidence of a transfusion reaction was found. The graft was replaced with one of another material and the rest of the patient's hospital course was unremarkable. Case 4: At another hospital, on 1/20/84, a 70-year-old-man underwent aortic bifurcation grafting with a Meadox double velour knitted 18 X 10 mm graft (lot #081010). Soon after restoration of flow SVR fell, cutaneous erythema occurred, and excessive blood loss ensued through the graft's interstices. The patient was assumed to have a transfusion reaction and was given diuretics and epinephrine. Over the next 2 1/2 weeks, 500 - 1000 mg of iv epinephrine was required every 24 h to maintain SVR. The patient died of ARDS. Graft material was not microscopically examined at autopsy. Case 5: After case 3 occurred, the authors obtained a list from the manufacturer of purchasers of lot K8B 12 X 6 mm Milliknit grafts. Upon calling one institution that had purchased 18 of these, we learned of an operation the previous day that proceeded identically to Case 3. The surgeon stated he had to replace the graft with another type to restore normal SVR and hemostasis.

Laboratory Evidence of Anaphylactoid Reactions (from Cases 2 and 3). Patients 2 and 3 (and two control patients undergoing similar operations) were participating in a study in which blood samples were obtained before and shortly after graft replacement (before major bleeding occurred). With patient permission, blood from those studies was diverted to evaluate the possibility of a reaction to graft materials. After graft replacement, patients 2 and 3 had a 6- and 35-fold increase in thromboxane B2 that did not occur in either of the two control patients. Histamine levels were markedly elevated in patient 3, but no alteration in PF4, leukotrienes, or 6-KETO $PGFFf_{1\alpha}$ was noted. Not enough plasma was available to evaluate these substances in patient 2. Patients numbered 2 and 3 had substantial increases in C3a after graft insertion. In patient 3, there was a 50-fold increase in kallikrein after the graft was inserted with return to normal after graft removal. Serum from patient 3 caused activation of kallikrein in vitro. No such increase occurred in the plasma of control patients.

Discussion. Bleeding after vascular graft replacement is most often attributed to surgical technique. In all five of these cases, consumption coagulopathy occurred, triggered we believe by contact activation of plasma by graft material. These anaphylactoid reactions were initially manifest by persistently decreased SVR and erythema followed by consumption coagulopathy. It is important to recognize such reactions quickly, as survival appears to depend on rapid graft replacement.

Title: ETHANOL REVERSAL WITH NALOXONE

Authors: John M. Saddler, M.B.ch.B., MFM James, FFARCS, R.C. Cork, M.D., Ph.D.*

Affiliation: Department of Anaesthetics, The University of Zimbabwe, Harare, Zimbabwe and
*Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724

Introduction

Alcohol exerts analgesic effects similar to those of morphine for applied somatic pain. Observations that naloxone can reverse ethanol coma have led to speculation that the two drugs may act through similar pathways.[1] To study this idea, the effect of naloxone on pain threshold, short term memory, motor skills and reaction time in subjects treated with morphine or ethanol was tested.

Methods

The study was approved by the Ethics Committee. Eight subjects were subjected to the experimental procedure twice, receiving at random morphine on one occasion, and ethanol on the other, at an interval of two weeks. Pain threshold was tested by the application of pressure to the bare area of the tibia. Motor skills were assessed by the use of a pursuit rotor on which a pointer had to be kept on an eccentrically rotating disc over a period of one minute. Deviations from this disc were electronically scored. Re-action time was measured as the time taken to press the correct button to extinguish one of three different colored lights expressed as a mean of ten attempts. A digit span recall test was used to assess memory, using computer generated random numbers of 5 digit lengths. If at least one out of three attempts was correct, the digit span was increased by one to the point of failure. The subject was scored by multiplying the number of correct responses by the digit span at each level. Subjects were permitted as much practice as was necessary to achieve consistant scores on each test to minimize practice effects.

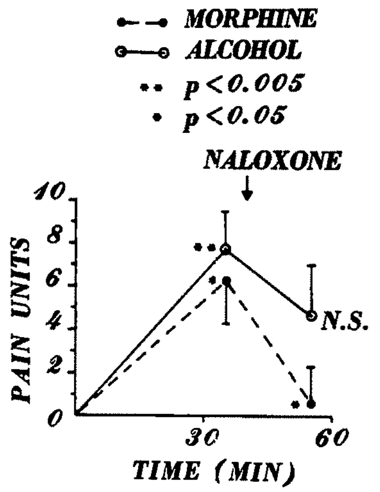
After starting an i.v. line, baseline measurements of all tests were performed. Alcohol subjects were given a loading dose of 0.75 ml/kg ethanol as a 10% solution in saline, followed by a pharmacokinetically predicted steady state infusion rate of 0.0025 ml/kg/min. Blood ethanol levels were estimated by accurate analysis of ethanol content of expired air. Morphine subjects were given a loading dose of 0.2 mg/kg followed by an infusion of 0.004 mg/kg/min. It was not possible to assay morphine levels. The loading dose was given over 20 minutes, and the steady-state infusion over a further 10 minutes. A second set of measurements were then made. Naloxone 0.015 mg/kg was then administered i.v. and after a further 10 minutes, the final set of readings recorded. The infusion was maintained throughout.

Results

There was an increase in pain threshold of 7.7±1.7 pain units in the alcohol group and of 6.1±1.5 pain units in the morphine group ($p < 0.005$ for both groups). Following naloxone, there was a significant reduction in pain threshold to baseline levels in the morphine group ($p < 0.005$). There was a small fall in the alcohol group (3.1±2.4 pain units) but this did not reach statistical significance. The difference between groups was significant at the 0.05 level.

Ethanol caused a significant impairment of motor skills. The mean error score increased from 29.75±7.8 to 90.5±21.1 after ethanol administration ($p < 0.05$). Naloxone reduced this to 44.1±13.9 ($p < 0.05$). Morphine produced a smaller non-significant rise from 22.2±8.9 to 32.9±6.7. Following naloxone, there was a significant improvement to a score of 17.5±5.6 ($p < 0.01$). The difference between baseline and post-naloxone scores was not significantly different.

Neither drug-impaired memory or reaction time and naloxone was without effect.



Discussion

Ethanol analgesia may be partially reversed by naloxone, but to a significantly smaller degree than the reversal of morphine-induced analgesia. Naloxone produced significant reversal of the motor skills impairment resulting from ethanol infusion and also improved the scores following morphine infusion, although morphine had only a minor effect on coordination. These results suggest that the analgesia produced by ethanol is at most only partly mediated through the opioid pathway. The effect of naloxone on some of the characteristics of ethanol intoxication are more likely to be mediated through a non-specific action rather than via the opioid system.

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Title: NEUROMUSCULAR AND CARDIOVASCULAR EFFECTS OF BW B1090U IN ANESTHETIZED VOLUNTEERS

Authors: J.J. Savarese, M.D., H.H. Ali, M.D., S.J. Basta, M.D., N. Sunder, M.D., R.F.P. Scott, M.D., M. Gargarian, M.D., M. Gionfriddo, B.A., J. N. Weakly, Ph.D.*, A.G. Batson, B.S.*
Affiliation: Anesthesia Laboratories, Department of Anesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA and Medical Department, Burroughs Wellcome Co. Research Triangle Park, NC*

Introduction: BW B1090U, a new nondepolarizing relaxant, has a fast onset and a short duration of action lacks cumulative effects, and has a neuromuscular:cardiovascular safety margin of about 10:1 in animals[1]. For these reasons, a trial in human volunteers was felt warranted and was undertaken to construct approximate dose-response curves for neuromuscular and cardiovascular responses prior to testing in patients undergoing surgical procedures.

Methods: Eighteen male volunteers (ages 21-40) gave written informed consent. No premedication was administered. Arterial and venous cannulae were placed under local anesthesia. General anesthesia was induced with fentanyl (6-8 μg/kg) and thiopental (6-8 mg/kg), and the trachea was intubated under topical anesthesia. Ventilation was then controlled with nitrous oxide and oxygen (4L/2L) to maintain end-tidal CO_2 in the range of 30-35 mmHg. The ulnar nerve was stimulated via needle electrodes with supramaximal pulses to elicit the single-twitch adductor response of the thumb at 0.15 Hz. Arterial pressure, heart rate (via tachograph) and twitch were simultaneously recorded. After 15 minutes stable baseline, BW B1090U was injected as a rapid bolus (5-10 sec) into a rapidly running I.V. stream.

Volunteers #1 and 2 received graded doses spaced 15-30 min apart until 10-20% block of the twitch was achieved. Volunteers #3-18 each received a single bolus dose of BW B1090U. Dosage was increased in a graded sequence in volunteers #3-18 from 0.04 to 0.25 mg/kg. In volunteers #7-18, a second dose of BW B1090U was given after complete recovery from the first dose in order to re-establish full paralysis of the twitch. When 5% twitch recovery was achieved from this dose, an infusion of BW B1090U was begun. The infusion rate was controlled to maintain 90-99% twitch depression for 30-120 minutes. Infusion duration (30, 60, 90 and 120 minutes) was increased sequentially in pairs of volunteers. Volunteers #13-18 received the longest infusions (120 min). When the infusion was terminated, spontaneous recovery was observed in the odd numbered individuals. In even numbered volunteers, antagonism of residual blockade was tested by administering neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg).

Results were analyzed where appropriate by linear regression on probit values, by analysis of variance and by student's t-test.

Results: The ED95 is approximately 0.07 mg/kg. The duration of action (injection to 95% return of twitch) was 26.3 minutes at 0.1 mg/kg, the lowest dose producing 100% block. Neuromuscular data are summarized in Table 1.

Table 1

Dose (mg/kg)	n	% Block	Onset (min)	Duration (min)*
0.04	2	62	4.0	15.6
0.06	2	70	4.0	20.6
0.08	2	75	4.3	14.6
0.10	2	100	3.8	26.3
0.15	2	100	2.7	34.6
0.20	3	100	2.5	29.0
0.25	3	100	1.7	32.0

* injection to 95% of control twitch

Spontaneous recovery time (5-95%) averaged 15.8 minutes for all doses above 0.08 mg/kg (n=10). Corresponding time after 1 to 2 hour infusions (n=5) averaged 16.9 min. Similarly, recovery times (25-75%) averaged 7.5 min and 6.9 min after all single-bolus doses producing 100% block (0.1-0.25 mg/kg) and after 1-2 hour infusions respectively. The differences were not significant. In six cases where neostigmine was given to antagonize residual block at the end of infusions, reversal from an average twitch height of 20% to 95% required 5.6 min. The 25-75% recovery time averaged 2.6 min.

Cardiovascular Effects: At up to 0.15 mg/kg, changes in heart rate and arterial pressure were less than 5%. At 0.2 and 0.25 mg/kg (approximately 3-4xED95), decreases in arterial pressure and increases in heart rate were noted. In the six individuals who received these highest doses, heart rate increased an average of 25% and arterial pressure decreased an average of 25%. These changes were brief, lasting 1-3 min.

Conclusion: BW B1090U is a potent nondepolarizing neuromuscular blocking drug with short duration of action, minimal cumulative effect, and reasonable cardiovascular safety. For these reasons, further studies in surgical patients seem justifiable.

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Title: DOES MORPHINE ANALGESIA PRODUCE CHANGES IN PERIPHERAL NERVE FUNCTION IN CATS?

Authors: M Senami, M.D., M Aoki, M.D., LM Kitahata, M.D., Ph.D., O Yuge, M.D., Ph.D., and JG Collins, Ph.D.

Affiliation: Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510

Introduction. Opioid analgesics act at both spinal and supraspinal sites, but it is still widely assumed that they do not alter conduction in peripheral nerves. However, opioid binding sites have been demonstrated on dorsal roots in adult mammals (1). Jurna and Grossmann (2) reported that the intra-arterial injection of morphine (2 mg/kg) significantly reduced the compound action potential of A-delta and C fibers of cat's sural nerve in vivo, but these results have not been verified by others. The purpose of the present study was to determine if the direct application of morphine on peripheral nerve caused detectable changes in the compound action potentials of A-beta, A-delta, and C fibers.

Methods. The superficial radial nerve was exposed in three sites on the forelimb of decerebrate cats. The skin around each exposure site was mounted on a small metal ring forming a well that provided access to the nerve. Paraffin film was placed beneath the nerve to shield it from the surrounding tissue. Silver electrodes were placed in the proximal well for stimulation and in the distal well for recording. The central well, which was used for drug administration, was sealed with paraffin film in order to retain moisture and heat. The nerve in the outer wells was covered with a paraffin oil pool that was maintained at 37 ± 0.5°C. Stimulation was performed with single rectangular pulses of 0.05 msec duration, 1 Hz for 16 seconds. Following control studies, morphine sulfate (5 mg/ml or 10 mg/ml, each 0.1 ml/kg in 37°C physiologic saline) was placed directly on the nerve in the central well and A-beta, A-delta and C fiber compound action potentials were observed at 5, 15, and 30 minutes. Sixteen consecutive responses were stored and averaged by a Nicolet Instrument Computer (Model 1074). The areas under the compound action potentials of A-beta, A-delta and C fibers were determined by measurement of the negative components of these potentials and compared with control values. Conduction velocities were also measured.

Results. The conduction velocities of A-beta, A-delta and C fibers were not significantly changed within 30 minutes after the administration of either 5 or 10 mg/ml (0.1 ml/kg) of morphine sulfate. The areas under the compound action potential of the A-beta and A-delta fibers were not significantly changed either. The only statistically significant change ($p < .01$) was a relatively small increase in area under the C fiber compound action potential 15 minutes after 10 mg/ml of morphine (see Table 1).

Discussion. The results of the present investigation indicate that morphine administered directly on the superficial radial nerve of cats did not reduce the size of the compound action potentials or the conduction velocities of A-beta, A-delta and C fibers at the concentrations of 5 and 10 mg/ml (0.1 ml/kg). These results are not in agreement with those of Jurna and Grossmann (2). The discrepancy may be due to a different route and dose of drug administration or different temperatures at which the nerves were studied.

These findings reinforce the concept that analgesia following systemic opioid administration is unlikely to be due to opioid effects on primary afferents in the periphery. However, these findings do not rule out the possibility that opiate receptors on the dorsal roots are important as sites of action following spinal opioid administration.

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Table I.

Integrated negative component of the compound action potential (% control ± S.D.)

5 MG/ML 0.1 ML/KG MORPHINE

	5 min	15 min	30 min.
A-beta (n=4)	100.1±4.6	97.6±5.8	101.6±6.5
A-delta (n=4)	94.1±9.3	91.4±9.5	93.8±5.6
C (n=4)	94.9±10.6	95.0±7.7	97.4±10.6

10 MG/ML 0.1 ML/KG MORPHINE

	5 min	15 min	30 min.
A-beta (n=8)	100.5±10.3	101.8±10.5	101.8±20.3
A-delta (n=8)	97.3±14.6	106.6±26.2	96.5±13.8
C	106.5±12.2	110.2±5.7	105.9±8.0

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Title: DECREASED CSF PROTEIN DURING PREGNANCY AS A MECHANISM FACILITATING THE SPREAD OF SPINAL ANESTHESIA

Authors: AP Sheth, M.D., DL Dautenhahn, M.D., L Fagraeus, M.D., Ph.D.

Affiliation: Department of Anesthesiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73152

Introduction. Hormonal, chemical, as well as mechanical changes have been implicated to explain facilitated spread and increased potency of local anesthetic in epidural and subarachnoid spaces during pregnancy.[1] Cerebrospinal fluid of pregnant, postpartum, and non-pregnant patients was studied for biochemical changes, specifically CSF protein concentration, which could affect the action of local anesthetics.

Methods. The study was evaluated and approved by the Committee on Human Research at the Health Sciences Center. Spinal fluid was collected from 6 non-pregnant women between 20-40 years age group, 6 early pregnant patients between 12-17 weeks of pregnancy who required cerclage, 11 term pregnant patients for elective C-section, 23 postpartum patients who required tubal ligation. In patients selecting spinal anesthesia in the above mentioned groups, one ml of spinal fluid was obtained prior to introduction of local anesthetic in the subarachnoid space. CSF was analyzed for total protein content using a DuPont Automatic Clinical Analyzer #3. All patients entered in this study had clear spinal fluid. Patients with medical problems were not included in study. Comparisons of each group with the control (non-pregnant) group were performed utilizing analysis of variance followed by unpaired t tests.

Table I.

Change in CSF Protein During Pregnancy and Postpartum

Group	CSF Protein (Mean±SEM, mg%)	Change % of Control
I. Non-pregnant (Controls)	27 ± 2.4	Control
II. Early pregnant	19.8 ± 2.3 (P<.05)*	-28
III. Term pregnant	19.2 ± 0.8 (P<.05)*	-30
IV. Early postpartum 0-18 hrs.	16.3 ± 1.9 (P<.01)*	-40
V. Postpartum 19-36 hrs.	24.7 ± 1.7 (P=0.39 N.S.)	-11
VI. Postpartum 37-54 hrs.	33.5 ± 3.7 (P=0.11 N.S.)	+22
VII. Postpartum >55 hrs.	43.5 ± 5.5 (P<.001)*	+58

*Significantly different from the non-pregnant control group (Group I).

Results. CSF protein concentration in different groups are shown in the table. CSF protein was significantly lower in early pregnant, term pregnant and 0-18 hours early postpartum patients compared non-pregnant control group. Between 18 and 36 hours postpartum, the CSF protein returned close to the control level but continued to exhibit a linear increase over time, ($r = .83$, $P<.001$) with significantly higher ($P<.001$) than control protein levels in the fluid samples taken more than 54 hours postpartum.

Discussion. In pregnancy, plasma protein decreases from 8.8 g/100cc to 7.55 g/100cc.[2] Changes are seen starting early in pregnancy. Similar changes could be expected in CSF protein.

Plasma buffer base decreases from 47 mEq/L to 42 mEq/L in pregnancy[3] as a result of decrease in Hb, HCO_3 and protein. CSF buffer base would be expected to decrease similarly due to a decrease in HCO_3[4] and a decrease in protein.

Although the protein concentration in CSF is much lower than in blood, the CSF concentration is sufficient to influence the dissociation of local anesthetic in spinal fluid by:

1) Affecting buffer capacity. Local anesthetic agents are salts that need buffer to convert to the base form for transport across membranes and into C.N.S. and circulation. Decrease buffer capacity may allow local anesthetics to remain a salt for a longer time and therefore stay longer in the area of injection. This will give time to spread further within anatomic tissue planes and increase dermatomal spread. It will also increase time to complete analgesia. 2) The lower concentration of protein in the CSF during pregnancy and the early postpartum period will bind less local anesthetic and therefore may increase the active, unbound form of local anesthetic available for blocking action in the subarachnoid space. Considering the lower volume of distribution in CSF and the small dose of local anesthetic used in subarachnoid anesthesia, such reductions in CSF protein may be a contributing factor in the apparent increase in potency of local anesthetics in the subarachnoid and epidural spaces during pregnancy and the early postpartum period.

In conclusion the temporal pattern of protein reduction in early pregnancy, term pregnancy and early postpartum match the temporal period of pregnancy related changes in potency of local anesthetic. Our results suggest that decreased protein concentration in CSF increases local anesthetic potency by reducing binding of local anesthetic in CSF and reducing buffer base in CSF.

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Title: OBSTETRICAL ANESTHESIA FOR PATIENTS WITH GENITAL HERPES: A RETROSPECTIVE STUDY

Authors: R. Sheth, M.D., S. Ramanathan, M.D., M. Durtzman, B.S., H. Turndorf, M.D.

Affiliation: Dept. of Anesthesiology, New York University Medical Center, New York, NY 10016

Introduction: Patients with genital herpes infections (HSV) often require anesthesia for cesarean section (CS) performed to minimize neonatal involvement.[1] The neurotropic herpes virus is known to persist in sensory ganglia and postganglionic fibers. There are known cases of neurologic relapses of herpes zoster following regional anesthesia.[2] General anesthesia (GA) may also be hazardous in patients with viral infections because anesthetics such as N_2O may be immunosuppressants.[3] In addition, pregnancy may be associated with immunosuppression.[4] This report describes our experience with regional and GA in patients with HSV infections. Our review of literature showed that there is only one report of use of lumbar epidural anesthesia (LEA) which appeared in the form of a letter to the editor.[5]

Methods: The total number of patients with HSV infection was 56 in the last 5 years in our institution. Twenty-three received GA and the remaining 33 LEA. Some members of the anesthesia attending staff in our institution used GA because they felt LEA was contraindicated in these patients. Anesthesia was induced using thiopental (3 mg/kg body weight). Trachea was intubated under succinylcholine induced muscle paralysis. Maintenance was done with N_2O (50 to 60%) in O_2. Muscle relaxation was maintained with d-tubocurare (0.3 mg/kg). Reversal of muscle paralysis was achieved using a mixture of atropine and neostigmine. All patients were extubated in the operating room uneventfully. LEA was induced to T4 level by injecting lidocaine 1.5% with epinephrine 1:200,000 through a Portex epidural catheter inserted through the L3-L4 or L2-L3 intervertebral space. All patients received prophylactic hydration of 1200 ml of Ringer's lactate solution. Left uterine displacement was maintained. Hypotension was promptly treated with 5 mg injections of ephedrine. Patients inhaled 0.5% FIO_2. After the delivery of the infant, diazepam (5 to 10 mg) or fentanyl (50 to 100 ug) were used for sedation as needed. Twenty-three patients required intravenous sedation. All patients were kept in isolation in accordance with the hospital policies. The postoperative course was reviewed for the presence of symptoms and signs of encephalitis (headache, persistent unexplained pyrexia > 102° F), meningitis (signs of meningeal irritation, pyrexia) or the development of new lesions and/or flare-up of the existing ones. Nursery course of all babies was also reviewed for the presence of any herpetic involvement.

Results: There were 20,112 deliveries in the study period in our institution. The different sites of HSV lesion, and the frequency of positive HSV isolation are shown in the table. One patient from the epidural group was given dexamethasone to promote fetal lung maturity. Although her lesions were completely healed at the time of delivery, she had recurrence in the immediate postnatal period. Another patient was on 5 mg of prednisone po for idiopathic thrombocytopenic purpura. Her platelet count was normal at the time of delivery. A GA was attempted but was abandoned because of difficult intubation. The procedure was done under LEA. This patient developed pyrexia of > 105° F which was later shown to be due to staphylococcal endometritis with positive lochial and blood cultures. None of the other patients who received GA or LEA developed any neurologic or anesthetic complications. Two neonates (one from each group) developed physiologic jaundice. All other neonates had uneventful nursery course.

Table:

	GA (n=23)	LEA (n=33)
I. Site of lesion		
a. genital	15	15
b. back and buttocks	3	3
c. extragenital (excluding b)	1	2
d. healed	4	14
II. Isolation of HSV		
a. positive in the last one month	7	13
b. positive in the first 8 months	4	3
c. negative in the last one month	4	14
d. Report not available	9	5

Legend: The site of lesions add up to 34 in the LEA group because one patient had both a and b. The discrepancy in the total in the isolation frequencies in both GA and LEA is due to some patients converting from category IIb to IIc during the course of pregnancy.

Discussion: Our data show that 1) both GA and LEA are safe in the presence of secondary (recurrent) HSV infection and therefore the choice of anesthetic should be based on 1) patient's preference and 2) demands of the situation. LEA should not be denied to patients who wish to remain awake during the procedure. It is to be noted that these results apply only to secondary HSV infection and not to the primary HSV, which is more frequently associated with extensive neurologic sequelae.

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Title: INCREASE IN MINIMUM ALVEOLAR CONCENTRATION (MAC) OF HALOTHANE BY LAUDANOSINE IN RABBITS

Authors: W-Z Shi, M.D., M. R. Fahey, M.D., D. M. Fisher, M.D., E. I. Eger, M.D., C. Canfell, M.S., R. D. Miller, M.D.

Affiliation: Department of Anesthesia, University of California, San Francisco, California 94143

Introduction. Laudanosine, one of the major metabolites of atracurium, was demonstrated in 1899 to cause central nervous system (CNS) excitation in the rabbit.(1) This study was carried out to determine whether the CNS excitation from laudanosine would alter the minimum alveolar concentration (MAC) of halothane in the rabbit.

Methods. Fifteen non-fasting, unpremedicated New Zealand white rabbits were studied. Anesthesia was induced with halothane and oxygen via a mask, and tracheostomy was performed. Anesthesia was maintained with 1.0% inspired halothane in oxygen and ventilation was controlled to maintain P_aCO_2 at 35-40 mm Hg. Temperature was maintained with surface warming at 39°C. Carotid artery cannulation was done for blood pressure measurement and for sampling blood; an ear vein was cannulated for laudanosine administration. A unilateral fronto-occipital electroencephalogram (EEG) was obtained using subcutaneous needle electrodes. Five rabbits were given 3 mg/kg of laudanosine (iv bolus) and blood samples were taken at various intervals over the next 4 hrs. Plasma levels of laudanosine were determined by ion-exchange liquid chromatography(2), and the data were fit to a two-compartment pharmacokinetic model. Ten rabbits were used to determine the MAC of halothane using the method of Eger et al.(3) Laudanosine was infused into 8 of these 10 rabbbits to reach 3 steady-state plasma levels of 200(I), 400(II) and 800(III) ng/ml; the infusion technique was calculated using the method of Wagner(4) and the pharmacokinetic results from the first 5 rabbits. During steady-state conditions, MAC for halothane was determined and compared to control MAC by repeated measures analysis of variance ($P < 0.05$). Steady-state laudanosine plasma levels were confirmed by obtaining blood samples before and after MAC determinations. Finally, the MAC for halothane was determined 2 hrs after the laudanosine infusion was discontinued, The remaining 2 rabbits were studied under identical conditions except that saline without laudanosine was infused.

Results. The pharmacokinetic variables for the two-compartment model for laudanosine are shown in Table 1. The laudanosine infusion protocol achieved levels of 234 ± 56 (I), 457 ± 66 (II) and 873 ± 105 (III) ng/ml (±SD). The halothane MAC data are shown in Table 2. MAC values at the II and III steady-state levels were statistically greater than control but not different from each other. Once the laudanosine infusions were terminated, MAC values returned to control levels by 2 hrs. No change in the MAC of halothane was observed in the rabbits receiving saline infusions without laudanosine. EEG monitoring showed seizure activity in rabbits given 3 mg/kg of laudanosine, but there were no abnormal EEG findings in rabbits used for MAC determinations.

Discussion. This study clearly has shown that CNS stimulation by laudanosine can increase the MAC of halothane in the rabbit by as much as 30%. The lack of similar effects in rabbits given saline infusions and the return to control MAC values with termination of the laudanosine infusion definitively support this view. Peak laudanosine levels in man following a single dose of 0.5 mg/kg atracurium have been measured as high as 327 ng/ml.(2) Thus it may be possible for anesthetic requirement to increase in patients receiving atracurium for surgical relaxation, particularly if atracurium is administered for prolonged periods. The clinical manifestations of this increased anesthetic requirement may be masked by the paralysis from atracurium. Further studies must be done in man to investigate these possibilities.

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TABLE 1: PHARMACOKINETIC VARIABLES (mean ± SD)

$t_{1/2}\alpha$ (min)	$t_{1/2}\beta$ (min)	V_1 (L/kg)	Vd_{ss} (L/kg)	Clearance (ml/kg/min)
5.2 ±2.3	47.3 ±16.9	0.8 ±0.4	2.1 ±1.0	41.9 ±6.7

TABLE 2: MAC VALUES WITH LAUDANOSINE*

CONTROL	I	II	III
1.56	1.56(0)	1.86(18)	1.93(24)
0.83	1.04(18)	1.12(27)	1.17(33)
0.83	1.02(23)	1.22(47)	1.40(69)
1.39	1.42(2)	1.56(13)	1.57(13)
0.95	1.06(11)	1.20(26)	1.20(26)
0.86	0.86(0)	0.92(8)	0.92(8)
1.00	1.03(3)	1.17(17)	1.23(23)
1.19	1.24(4)	1.44(21)	1.60(34)
MEAN %	8	22	29

* = values are end-tidal concentrations of halothane with % increase over control in parentheses

TITLE: CORONARY ARTERY BYPASS GRAFT SURGERY WITHOUT CARDIOPULMONARY BYPASS

AUTHORS: G Silvay MD, BP Mindich MD, NL Burgess MD, D Girard MD, DM Thys MD, JA Kaplan MD

AFFILIATION: Departments of Anesthesiology and Surgery, The Mount Sinai School of Medicine, One Gustave Levy Place, New York City, New York, 10029

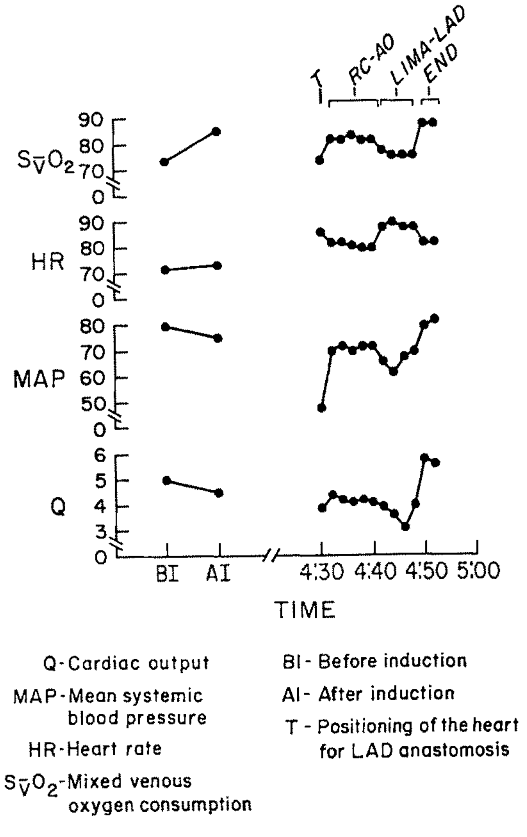
Introduction: The safety of myocardial revascularization (CABG) has been well established over the past decade. In an effort to reduce or eliminate the problems of excessive postoperative bleeding, neurologic dysfunction, and untoward reactions to heparin or protamine sulphate which occasionally are associated with cardiopulmonary bypass, selected patients have undergone CABG without cardiopulmonary bypass (CPB). The anesthetic management has been directed at providing optimal operating conditions while maintaining adequate hemodynamics.

Methods: Fifty-one patients (35 males, 16 females) aged 41 years to 84 years underwent CABG without CPB. Ten patients were failed angioplasty candidates; 5 were operated on as emergencies. Thirty-one patients received a single graft; 23 to the left anterior descending (LAD) coronary artery, and 8 to the right coronary artery (RCA). Eighteen patients received two grafts: LAD and RCA 14 patients; LAD and diagonal 4 patients. Two patients received grafts to the LAD, diagonal and RCA. Premedication included morphine sulphate 0.1 mg/kg and lorazepam 0.05 mg/kg. Arterial and venous pressures, heart rate, ECG leads II and V_5, cardiac output, and mixed venous oxygen saturation were monitored. In 25 patients anesthesia was induced and maintained with a combination of fentanyl 50-100 ug/kg, diazepam 0.4 mg/kg, and pancuronium 0.1 mg/kg. In 26 patients in addition to the intravenous drugs, a volatile anesthetic agent (halothane or enflurane) was used. High doses of beta-blockers have been used following early experiences with tachycardia and dysrhythmias during CABG without CPB. Therefore, after opening the pericardium the patients received propranolol 2.0-5.0 mg in 0.5 mg increments to slow the heart rate to 50-70 beats/min. If the patients maintained hemodynamic stability during the induction of anesthesia, opening of the pericardium and exposure of the coronary vessels, a coronary artery was occluded during a test period of one to two minutes to obtain all measurements and insure ECG and hemodynamic stability. The procedure was to be aborted and CPB instituted if the test was unsuccessful. If the ECG and hemodynamics were stable, CABG was performed without CPB. A period of 4-6 minutes was required for performance of the distal anastamosis. Following this, the proximal anastamosis was performed before proceeding to the next distal. In multivessel procedures, the totally occluded vessels were done first to supply collateral flow to the subtotally occluded vessels. Heparin was not utilized.

Results: Hemodynamic changes during a typical procedure are shown in the figure. It demonstrates a normal response to the coronary occlusion test (T), which all patients successfully passed. The addition of a volatile anesthetic agent appeared to have no influence on the hemodynamics intraoperatively, nor on the ultimate outcome of the procedure. All patients left the operating room in stable condition. Four patients were found on the postoperative electrocardiogram to have suffered a perioperative infarct, two of which were documented before surgery. One required vasoactive support, intraaortic balloon counterpulsation, reoperation, and subsequently died. There were no neurological, nor coagulation complications.

Discussion: CABG can be performed without CPB if the patients are carefully selected and properly managed. Optimal monitoring during the test period, to evaluate the hemodynamic response to surgical access to the LAD and manipulation of the beating heart, is needed for success of the procedure. This group of patients represent a special challenge to the anesthesiologist since they require continuous optimal monitoring and frequent perioperative pharmacologic interventions with beta-blockers, vasopressors, and vasodilators.

HEMODYNAMIC CHANGES



Title: NEUROMUSCULAR AND CIRCULATORY RESPONSES TO ATRACURIUM DURING ADMINISTRATION OF HIGH DOSE OF FENTANYL

Authors: C.T. Skourtis, M.D., C. Athanasiadis, M.D., H.H. Ali, M.D., D.G. Lappas, M.D., P. Mihelakos, M.D.
Affiliation: Anesthesia Service, Department of Anesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA 02114

Introduction: It has been demonstrated that atracurium in bolus doses of 0.3 or 0.4 mg/kg^{-1} produced minimal circulatory effects in cardiac surgical patients, who have received lorazepam (1-2 mg) and fentanyl (0.1-0.2 mg.i.v.).[1] However, neither the hemodynamic nor the neuromuscular effects of atracurium in patients receiving large doses of fentanyl have been evaluated. Thus, the present study was undertaken to evaluate the cardiovascular effects of atracurium and to obtain quantitative assessment of its neuromuscular effects in patients receiving large doses of fentanyl.

Methods: After obtaining approval of the institutional committee on human studies and informed consent, 10 patients, 40-60 years old scheduled for elective coronary artery bypass grafting (CABG) were studied in two equal groups (Group A and B). All patients had been receiving beta blockers which were continued until the time of operation. Patients were premedicated with morphine 0.1 mg.kg^{-1} and scopolamine 0.4 mg I.M., and lorazepam 1 mg p.o. Prior to induction of anesthesia, radial artery and pulmonary artery (thermodilution) catheters were placed for continuous monitoring and recording of systemic arterial (SAP), pulmonary arterial (PAP), pulmonary capillary wedge (PCWP) and right atrial (RAP) pressures (mm Hg). Heart rate (HR, b.min^{-1}) and rhythm were recorded from lead II and V4, and cardiac outputs (CO,l.min^{-1}) were measured by thermal dilution. Systemic (SVR) and pulmonary (PVR) vascular resistance (dyn.sec.cm^{-5}) were calculated by the standard formulae. Neuromuscular blockade was monitored by recording evoked thumb adduction in response to supramaximal ulnar nerve stimulation at the wrist (0.15 Hz). The time to 95% depression (onset time) was determined. Patients were given oxygen at FIO$_2$ I.0. After a stable baseline period, control measurements were obtained (phase I). A pretreatment dose of atracurium 0.05 mg.kg^{-1} was given in Group A and 0.1 mg.kg^{-1} in Group B. Approximately 5 minutes later, measurements were repeated (phase II) and an infusion of fentanyl (0.05 mg.kg^{-1}) was started in both groups. A bolus injection of 0.35 mg.kg^{-1} atracurium was given in Group A and 0.3 mg.kg.$^{-1}$ in Group B. Upon completion of the fentanyl infusion (4-5 min), hemodynamic measurements were repeated (phase III). Results were compared using student's t-test with p 0.05 being considered significant.

Results: There was no significant difference between the two groups with respect to control hemodynamic values. Atracurium in either pretreatment dose of 0.05 or 0.1 mg.kg^{-1} produced no significant hemodynamic changes (Table 1). There was no significant change in HR, PAP, PCWP, RAP, CO and PVR in either group throughout the study period. A significant decrease in mean SAP was observed in Group A following the administration of 0.35 mg.kg^{-1} atracurium (phase III) which was caused by a decrease in SVR, since SV did not change.

A 10% twitch tension depression was noted in 3 of the 5 patients in Group B after 0.1 mg.kg.$^{-1}$ atracurium. The time to 95% twitch depression in Group A and B was 3.02±1.2 min and 4.5±1.9 min respectively. Excellent intubating conditions were obtained in both groups following a total dose of 0.4 mg.kg^{-1} atracurium and rigidity was not observed during fentanyl administration.

Discussion: Contrary to previous reports,[1,2] our data indicates that atracurium in bolus injection of 0.35 mg.kg.$^{-1}$ in patients receiving large doses of fentanyl may cause significant decrease in SAP due to a fall in SVR. However, in doses of 0.3 mg.kg.$^{-1}$ no such hemodynamic alterations were observed. Therefore, it is the bolus dose of atracurium and not the total that matters.

Both pretreatment doses for atracurium caused no hemodynamic changes and prevented rigidity of fentanyl. However, the 0.1 mg.kg.$^{-1}$ dose resulted in a 10% twitch depression in 3 patients with slight agitation.

In both groups,the time to 95% twitch depression was shorter than previously reported. The prolongation of the time to 95% twitch depression in Group B may be due to the smaller dose (0.3 mg.kg.$^{-1}$) given, after the pretreatment. We conclude that atracurium in bolus doses of 0.3 mg.kg.$^{-1}$ has minimal hemodynamic effects in patients receiving high doses of fentanyl. Finally, should there be a pretreatment dose for atracurium, to speed the onset of atracurium the 0.05 mg.kg.$^{-1}$ is the most advantageous.

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Heart Rate	Phase I	Phase II	Phase III
Group A	60±8	58±9	52±6
Group B	58±7	57±10	62±12
Mean SAP			
Group A	92±11	95±16	67±18*
Group B	81±7	85±10	80±13
Cardiac Output			
Group A	4.2±.5	4.4±1	4.5±1
Group B	4.0±.5	4.0±.5	4.3±1
Systemic Vasc Resistance			
Group A	1641±249	1604±403	1107±408*
Group B	1541±262	1600±367	1437±330

*$p<0.05$

Title: EVENTS ASSOCIATED WITH INTRAOPERATIVE EVOKED POTENTIAL CHANGES
CORRELATION WITH POSTOPERATIVE NEUROLOGICAL STATUS

Authors: T Sloan, M.D., Ph.D., A Koht, M.D., A Ronai, M.B., B.S., Ph.D., JR Toleikis, Ph.D.

Affiliation: Northwestern University Medical School, Chicago, IL 60611

Introduction. Sensory evoked potentials (SEP) are monitored during operations on the spinal cord, brainstem and cerebral cortex. Information regarding the correlation of intraoperative changes and outcome is inferred from animal studies and supported by anecdotal observations in humans; controlled experimentation in man is presently not possible. The association of changes with outcome should also be partially determined by the cause of the SEP alteration. Deterioration associated with various anesthetic events or transient physiologic changes would be expected to produce less neurological injury than direct surgical trauma to the nerve tracts. This study was undertaken to evaluate the events associated with intraoperative SEP deterioration and the correlation of these events with the presence of postoperative neurological changes.

Methods. This study consisted of 475 adult cases (3/28/83-8/1/84) where SEP was used to monitor nerve tracts placed at risk during operations on the spinal cord (336 operations) or brainstem and cerebral cortex (139 operations) was approved by the Institutional Review Board. Standard unilateral stimulation and recording techniques were used to continuously monitor patients from induction to emergence of anesthesia. Many patients (notably in brainstem and cortical operations) were monitored with multiple techniques to allow multiple assessment of neural tracts at risk directly (i.e. from direct surgical manipulation) and indirectly (i.e. from physiological shifts such as hypotension). With spinal cord operations, recordings were taken separately from subcortical and cortical regions. SEP modalities used for these 475 operations included median nerve (248), posterior tibial nerve (270), common peroneal nerve (9), brainstem auditory (45), cortical auditory (8) and light emitting diode visual (52).

Anesthesia for these operations consisted of premedication with 0.4 mg IM atropine or scopolamine occasionally supplemented with IM morphine (spinal cases only) (0.1-0.15 mg/kg) or oral diazepam (0.05-1 mg/kg). Anesthesia was induced with thiopental and maintained with fentanyl (20-60 mcg/kg), and occasionally 0.2-0.5 MAC of halothane, enflurance or isoflurance. Ventilation with oxygen/air was controlled. Paralysis was maintained with pancuronium or d-tubo-curare (spinal cases only). Nitrous oxide was used only during skin closure and associated changes were not included in this study.

During monitoring, an abrupt shift in latency (increase of $\geq$ 10%) or amplitude decrease (to $\leq$ 50%) prompted evaluation for associated anesthetic, physiologic, technical or surgical events. Postoperative neural changes were detected by clinical exam and comparison of postoperative SEP recordings with recordings taken preoperatively.

Results. Sixty-five operations (13.7%) had intraoperative SEP deteriorations. As shown in Table 1, these were associated with anesthetic changes (2.5%) (e.g. change in inhalational agent, bolus delivery of thiopental or fentanyl), physiological shift (2.5%) (e.g. hypotension, temperature drop, tourniquet ischemia, positioning), technical problems (1.1%) (loss stimulating or recording electrodes, electrical noise, sychronization with patient's alpha rhythmn, equipment malfunction), or associated surgical manipulation (7.6%) (e.g. direct manipulation of the nerve tracts or retractor pressure on nerves or major vascular structures).

All intraoperative deteriorations associated with physiological or technical changes were reversed after correction of the problem. Changes associated with anesthetic changes were reversed following readjustment of the inhalational agent or waiting for the bolus effect to dissipate. No postoperative neurological changes were noted in patients with these associated events.

As shown in Table 2, reversal of transient deteriorations associated with surgical events were always associated with good outcome (20 spinal, 6 cortical/ brainstem). Permanent intraoperative changes (4 with spinal, 6 cortical/brainstem) were always associated with postoperative changes.

Discussion. This study demonstrated good prognostic value of the permanent intraoperative SEP changes in spinal, brainstem and cortical operations. Multiple associated events, including physiological, anesthetic and technical changes were associated with SEP changes. When corrected, these alterations were associated with no neural damage. This suggests that attempts to constrain anesthetic changes and physiological shifts, as well as technical expertise, will allow focusing SEP monitoring on potential injurious surgical manipulation.

TABLE 1 Intraoperative Events Associated with SEP Deteriorations

Type of Operation	Spinal	Brainstem/ Cortical	Total
Total No. Cases	336	139	475
Anesthetic Change	9	3	12
Physiological Change	6	6	12
Technical Problem	3	2	5
Surgical Manipulation	24	12	36

TABLE 2 Association of Intraoperative SEP Changes with Outcome

Associated Event	No Neural Damage	Neural Damage
No SEP Change	410	0
Transient SEP Change		
Anes, Physiol, Tech	29	0
Surgical Related	26	0
Permanent SEP Change		
Surgical Related	0	10

Title: EFFECT OF THIOPENTAL ON BRAINSTEM AUDITORY EVOKED RESPONSES

Authors: RM Sommer, M.D., L Prichep, Ph.D., P Malarik, H Turndorf, M.D.

Affiliation: Departments of Anesthesiology and Psychiatry, New York University
Medical Center, 550 First Avenue, New York, NY 10016

Introduction: Intraoperatively recorded sensory evoked responses have been used extensively to assess the function of the brain and spinal cord during neuro, ophthalmic, cardiac, orthopedic and vascular surgery.[1] However few studies have documented the effects of anesthetic agents on the brainstem auditory evoked response (BAER). Using optimal digital filtering prior to averaging the BAER can be reliably recorded using sample sizes as small as 128, thus allowing accurate assessment of the BAER every 5-10 seconds. With this method we studied the BAER during thiopental induced anesthesia.

Methods: The human subjects research committee approved the protocol and all patients (pts) gave written informed consent. Eleven ASA I-II pts aged 22 to 40 years were studied. BAERs were recorded from FPz (+) in reference to left mastoid (LM,-), using silver/silver chloride pregelled, self-adhering electrodes. All electrode impedences were < 3000 ohms. Stimuli were ipsilateral auditory clicks delivered at an intensity of 75 dBSPL with contralateral masking of -30 dB, at a rate of 27.8/sec.

A method of optimal digital filtering implemented in the Brain State Analyzer (BSA) was used to record the BAERs.[2] With this method phase variance in the presence and absence of stimulation are compared and a digital filter defined. Subsequent samples are decomposed by spectral analysis (Fast Fourier Transform) and recombined (inverse transform) using the previously defined optimum filters. These signals thus reconstructed with "noise" selectively removed are then averaged, and are reproducible with sample sizes as small as 128-516.

Baseline measurements of the BAER were taken in the holding area. Patients were transferred to the operating room where intravenous catheterization was performed and ECG and blood pressure monitoring instituted. Patients were sedated with diazepam 0.1 mg/kg, fentanyl 1.5 mcg/kg and precurarized with d-tubocurarine 3 mg. After three minutes O_2 5 L/min was administered by tightly fitting mask through a circle system. Two minutes later anesthesia was induced with intravenous thiopental sodium 4-6 mg/kg and relaxation provided with succinylcholine 1.5 mg/kg. The patients were ventilated with oxygen and intubated 1 minute after induction. BAER's were measured before entering the operating room, after sedation and precurarization, after oxygenation and after induction of anesthesia.

Latencies for positive peaks I,II,III,V, and VII and negative peak VI were measured. In addition, the peak to peak amplitudes for positive V to negative VI and negative VI to positive VII were calculated. Data were analyzed by analysis of variance (ANOVA) and where significant by t-test comparing baseline measurement with the value of interest. $P<0.05$ was taken as significant.

Results: Latencies for positive peaks I,II,III,V, and VII and negative VI were not significantly altered by diazepam, fentanyl, d-tubocurarine, oxygen, thiopental sodium, or succinylcholine. (see table 1) The P V-N VI amplitude was also unaffected by these maneuvers. Induction of anesthesia with thiopental sodium and succinylcholine caused a significant decrease in the N VI-P VII amplitude.

Discussion: Peak latencies of the BAER were remarkably stable during sedation, precurarization, oxygenation and thiopental sodium induction of general anesthesia. This finding contrasts with the effect of enflurane which causes an increase in peak latency.[3] This study also demonstrates a significant and consistent decrease in peak-to-peak amplitude of N VI-P VII which is unrelated to the sedation, d-tubocurarine and oxygen effects and is only attributable to the induction of general anesthesia with thiopental sodium and succinylcholine. This change occurs in the setting of stable hemodynamics and demonstrates that thiopental anesthesia does not affect the BAER up to the level of the midbrain but significantly affects transmission through the thalamocortical projections.

TABLE 1 Peak Latencies (msec)

Peak	Step I	Step II	Step III	Step IV	±SD	ANOVA
P I	1.44	1.46	1.44	1.46	±0.24	NS
P II	2.50	2.43	2.45	2.64	±0.24	NS
P III	3.66	3.63	3.80	3.73	±0.33	NS
P V	5.52	5.50	5.64	5.71	±0.24	NS
N VI	7.91	7.93	8.21	8.33	±0.66	NS
P VII	10.17	10.41	10.57	10.20	±1.04	NS

TABLE 2 Peak to Peak - Amplitude(μV)

Peak-Peak						
P V-N VI	0.71	0.69	0.76	0.61	±0.20	NS
N VI-P VII	0.60	0.75	0.73	*0.24	±0.24	$P<$ 0.005

Legend: Step I= baseline data
Step II = fentanyl, diazepam, d-tubocurarine
Step III = O_2 5L/minute by mask
Step IV = Anesthesia induction thiopental,succinyl.
* = $P < 0.005$ step IV compared with step I by t-test
NS = not significant

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Title: HEMODYNAMIC COMPARISON OF NON-DEPOLARIZING MUSCLE RELAXANTS: A RANDOMIZED PROSPECTIVE STUDY

Authors: NJ Starr, M.D., DH Sethna, M.D., AF Samonte, M.D., FG Estafanous, M.D.

Affiliation: Department of Cardio-Thoracic Anesthesia, The Cleveland Clinic Foundation, Cleveland, Ohio 44106

Introduction. Non-depolarizing muscle relaxants have intrinsic cardiovascular effects that may influence hemodynamic responses to induction and intubation(1). The aim of the present study was to examine and compare prospectively the hemodynamic effects of atracurium (A), vecuronium (V), pancuronium (P), and pancuronium-metocurine mixture (PM) in patients undergoing elective coronary artery bypass surgery.

Methods. With informed consent, 40 patients (51±15 years, both sexes), were randomized to the four muscle relaxant groups of ten subjects each. Excluded were patients with hypertension, NYHA IV, valve disease, renal and liver disease, and those clinically unstable. Individual preoperative beta blocker and calcium antagonist therapy continued through the morning of surgery. Premedication was morphine sulfate (.11±0.02 mg/kg) IM, scopolamine 0.4 mg IM and nitroglycerin ointment (5-10 mg). Induction of anesthesia was standardized to fentanyl 50 mcg/kg, oxygen and muscle relaxant in the following doses: A: 0.4 mg/kg, P: 0.12 mg/kg; V: 0.12 mg/kg; and PM: (0.4 mg:1.6 mg/ml) 1 ml/10 kg. In each patient, 20% of the relaxant was given initially to prevent fentanyl-related muscle rigidity. The time taken to inject the relaxants (Mean: 113 sec), and time of induction (Mean: 197 secs) were recorded. Hemodynamics were recorded preinduction (control), 2 minutes post induction, 2 and 5 minutes post intubation. The ECG (V5) and patient's clinical condition were observed continuously. Hemodynamic measurements and derived indices were continuously recorded via a modified commercial computer.

This report is an analysis of the 37 patients studied so far; the number of subjects in each group are: A:10, V:9, P:8, PM:8. Data was analyzed using an analysis of variance test for unbalanced data with $p < 0.05$ as significant.

Results. There were no differences between the groups regarding age, sex, beta-blocker and calcium-antagonist therapy, and baseline hemodynamics.

There were no significant hemodynamic changes between groups at all measurement times, as shown in the table. No ECG ischemic changes were noted; one patient on A showed flushing during the study. Satisfactory relaxation for intubation was observed in all patients.

Discussion. This study demonstrates that equipotent doses of muscle relaxant, when given with fentanyl anesthesia, maintains hemodynamic stability in the normotensive patient with coronary disease. P, however, did produce a relatively higher increase in HR (up to 27%), although still statistically insignificant. The observed hemodynamic stability may have been due to the concomitant use of high dose narcotic, allowance of adequate time for induction (197 secs) and the exclusion of hypertensive or unstable patients. Duration of action, routes of metabolism and elimination, and cost remain as important factors to consider in the clinical choice of muscle relaxants.

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TABLE: HEMODYNAMIC MEASUREMENTS (M + SE)

	HR	MAP	PCWP	CVP	CI	SVR
Baseline						
V	72±5	100±4	8±1	15±3	2.5±0.1	1549±132
P	62±6	97±9	9±1	13±4	2.9±0.1	1285±181
A	65±7	99±7	9±1	15±3	2.8±0.2	1423±213
PM	73±6	91±5	6±1	12±3	2.8±0.2	1403±140
Induction: 2 mins						
V	71±6	101±5	10±2	20±1	2.5±0.4	1523±93
P	76±8	97±4	8±1	14±1	3.2±0.3	1225±132
A	66±8	92±5	12±1	15±1	3.0±0.4	1136±183
PM	80±7	85±8	10±1	12±1	2.9±0.3	1147±182
Intubation: 2 mins						
V	73±4	102±3	10±2	18±2	2.7±0.3	1511±126
P	79±4	103±4	8±1	14±2	3.3±0.2	1321±86
A	79±7	101±4	11±1	18±2	3.2±0.3	1249±112
PM	83±5	92±4	10±1	13±2	2.9±0.2	1341±92
Intubation: 5 mins						
V	66±7	99±6	9±12	18±29	2.5±0.4	1546±200
P	74±7	98±8	8±1	13±2	3.0±0.3	1334±115
A	66±8	95±5	11±1	17±2	2.9±0.3	1234±141
PM	76±7	90±5	9±1	13±2	2.7±0.3	1351±137

Abbreviations: HR: Heart rate (beats/min); MAP: Mean arterial pressure (mm Hg); PCWP: Pulmonary capillary wedge pressure (mm Hg); CVP: Central venous pressure (mm Hg); CI: Cardiac index (ml/min/m^2; SVR: Systemic vascular resistance (dynes/sec/cm^{-5}).

Title: ARRHYTHMIAS AND CONDUCTION DISTURBANCES RELATED TO SWAN-GANZ CATHETERIZATION

Authors: RL Stevenson, M.D., C Beattie, M.D., RC Jacobson, M.D.*

Affiliation: Department of Anesthesiology and Critical Care Medicine*, Johns Hopkins University School of Medicine, Baltimore, Maryland

Introduction. The insertion of a Swan-Ganz catheter has been implicated in past studies as a cause of transient arrhythmias. The incidence by different investigators has ranged from 1.2% to as high as 15% (1, 2) of all pulmonary artery catheterizations. Other investigators have described the onset of right bundle branch block during Swan-Ganz catheter insertion (3) as well as the development of complete heart block in patients who had a preexisting left bundle branch block conduction abnormality (4). The experience with these patients has been drawn from individual case reports or studies of limited numbers of patients with pre-existing bundle branch blocks. It is often felt that Swan-Ganz insertion should not be performed in patients with left bundle branch blocks unless the capability for pacing the heart is also available.

This study attempts to measure the incidence of arrhythmias and conduction changes occurring in patients having pre-operative insertion of a Swan-Ganz catheter. The incidence of conduction changes was also measured in a second group of patients with pre-existing bundle branch block to help determine if pacemaker insertion is needed before Swan-Ganz catheterization in this group.

Methods. In our hospital, cardiac surgical patients undergoing preoperative pulmonary artery catheterization (PAC) receive a 12 lead EKG immediately before catheter insertion. During insertion, EKG leads V_5 and AVF are continuously recorded along with systemic blood pressure and right sided chamber pressures. Using these records and hospital charts, we retrospectively analyzed 154 consecutive insertions for evidence of arrhythmias and conduction abnormalities before and during PAC. In addition, we retrospectively identified an additional 60 patients with preexisting RBBB or LBBB who underwent PAC. These records were analyzed for trifascicular block (complete heart block) during PAC. This study was approved by our departmental Human Studies Committee.

Results. See Table 1. The incidence of ventricular ectopy during PAC was high. 112 patients (73%) had PVC's and 23 (15%) had ventricular tachycardia during PAC. Ventricular ectopy did not persist in any patient. There was no association between ventricular ectopy and EKG rhythm, preoperative medication, serum potassium, or operative procedure by Chi Square anaylsis.

Five patients (3%) developed RBBB during PAC. In all five patients, RBBB was transient, lasting less than one minute. None of the 154 patients developed trifascicular block, or complete heart block during PAC. Our subsequent review of 29 patients with LBBB and 31 patients with RBBB revealed no episodes of trifascicular block during PAC.

Discussion. Our study indicates that PVC's and VT occur frequently during PAC. However, these arrhythmias were transient and did not result in hemodynamic impairment.

RBBB occurred transiently in 3% of 154 patients studied. None of 29 patients with pre-existing LBBB developed trifascicular block during PAC. We conclude that the risk of TFB during PAC is low, although a precise estimate of risk would require a larger sample size. In view of the low incidence of TFB, routine insertion of a pacing catheter prior to PAC seems unwarranted.

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TABLE 1

	Before Insertion	During Insertion
Normal PR Interval	124	125
1° AVB	12	11
2° or 3° AVB	0	0
Atrial fibrillation	17	17
Paced Rhythm	2	3
LBBB	4	4
RBBB	7	12
ECTOPY:		
None	139	42
PVC's	15	112
Ventricular Tachycardia	0	23

Title: IN VITRO DEGRADATION OF ATRACURIUM IN HUMAN PLASMA

Authors: RL Stiller, Ph.D., DR Cook, M.D. and S Chakravorti, Ph.D.

Affiliation: Departments of Anesthesiology and Psychiatry, University of Pittsburgh
School of Medicine, Pittsburgh, PA 15261

Introduction: Atracurium, a new nondepolarizing muscle relaxant, spontaneous decomposes via Hofmann elimination and is metabolized by nonspecific esterases-dual pathways. A potential end-product of both pathways is laudanosine. In previous studies we (1) and others (2) noted that the degradation of atracurium was several-fold faster in plasma than in buffer (at the same pH and temperature). We were interested, therefore, in determining the relative role of each pathway in the in vitro degradation of atracurium in buffer and in human plasma at various pH and temperatures.

Methods. Atracurium 2.5 nmoles ml^{-1} (3000 ng ml^{-1}) was added to 10 ml of Sorensen buffer (pH 7.3) or to 10 ml of fresh human plasma (pH adjusted to 7.3). The samples mixed with atracurium were incubated at 37°C; at 20 minute intervals for 180 minutes aliquots (0.4 ml) were withdrawn and placed in an acid medium. Atracurium and laudanosine were determined at each time by sensitive, specific HPLC assays (1). Dilutions (1:1, 1:2, 1:4) of human plasma and buffer were made and "spiked" with atracurium (as above). In addition, 30 umoles/ml of tetraisopropylpyrophosphoramide or disopropylfluorophosphate, both esterase inhibitors, were added to additional plasma samples "spiked" with atracurium (at the same pH and temperature). Atracurium and laudanosine were measured at the same time intervals. Since other metabolites of atracurium were not available to us, quantitative analysis of them is not possible.

Results. Atracurium (2.4 nmoles/ml) was inactivated in Sorensen buffer (pH 7.3, 37°C) at a linear rate; the mean half-life for atracurium was 40 (± 3 SD) minutes. The mean concentration of laudanosine at 20, 40, 60 and 180 minutes was 0.6, 1.5, 1.5, 4.2 nmoles/ml, respectively.

Atracurium (2.4 nmoles/ml) was inactivated in human plasma (pH 7.3, 37°C) at a linear rate; the mean half-life for atracurium was 19 (+1.5) minutes. The mean concentration of laudanosine at 20, 40, 60 and 180 minutes was 1.5, 3.5, 4.0, and 5.1 nmoles/ml, respectively. With serial dilution of plasma, the half-life of atracurium progressively increased and approached that of buffer alone; the concentration of laudanosine at 20 minutes progressively decreased. With the addition of esterase inhibitors to plasma the rate of atracurium decrease and laudanosine increase approached that of buffer alone.

Discussion. Under physiologic conditions atracurium is continually undergoing inactivation. Although a dual pathway for inactivation of atracurium has been proposed, the role of each pathway (route) is unclear. However, it appears that certain plasma components accelerate the inactivation of atracurium. Nonenzymatic inactivation (Hofmann elimination) of 1 nmole/ml atracurium can produce 1 nmole/ml of laudanosine and a diacrylate-laudanosine moeity; the diacrylatate-laudanosine moeity is further inactivated to another 1 nmole/ml of laudanosine and the residual diacylate bridge moeity. Thus, each atracurium molecule can produce 2 laudanosine molecules. On the other hand, ester hydrolysis of atracurium can produce either a monoquaternary alcohol or monoquaternary acid. The quaternary alcohol can be inactivated by ester hydrolysis to the acid or by Hofmann elimination to laudanosine (3).

Our data demonstrate that laudanosine is the major end-product of both pathways. Plasma constituents that are limited by potent esterease inhibitors or by dilution accelerate the inactivation of atracurium. Most likely, nonspecific aliesterases rapidly metabolize atracurium to the monoquaternary alcohol which in turn is inactivated to laudanosine. Pseudocholinesterase activity has no effect, per se, on atracurium inactivation (2). The ester hydrolysis route of atracurium inactivation is, thus, more important than the Hofmann elimination pathway under physiologic conditions in normal patients. Redistribution and elimination of atracurium also play a role in in vivo kinetics. Severe liver failure or renal failure has little effect on atracurium kinetics (4). In the absence of nonspecific esterases, atracurium is inactivated by Hofmann elimination; this route is a "safety-net" in the use of atracurium in patients with severely impaired liver or renal function.

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Title: FENTANYL VS ETOMIDATE PLUS FENTANYL FOR ANESTHETIC INDUCTION IN HIGH RISK PATIENTS

Authors: R. J. Stockham, M.D., T. H. Stanley, M.D., F. Groen, Drs., S. T. Gillmor, R.N., N. L. Pace, M.D., and K. King, M.D.
Affiliation: Department of Anesthesiology, University of Utah School of Medicine and Veterans Medical Center, Salt Lake City, Utah, 84132

Introduction: Fentanyl has become popular as an anesthetic induction agent in high risk patients because of its rapid onset of action and minimal hemodynamic effects. However, induction with fentanyl is often associated with chest wall rigidity, sometimes interfering with adequate ventilation, and a high incidence of postoperative respiratory depression. Etomidate is a new, rapid acting, sedative/hypnotic induction agent which also has been associated with minimal cardiovascular and respiratory depression. Unfortunately, etomidate often causes pain on injection, myoclonus, and postoperative nausea and vomiting. While these side effects can be reduced by pretreatment with fentanyl, the hemodynamic consequences of mixing these agents in high risk patients have not been carefully evaluated. The purpose of this study was to compare hemodynamics and side effects during induction of anesthesia with high dose fentanyl with those of a combined fentanyl-etomidate induction in patients with significant cardiovascular disease.

Methods: The study was approved by the institutional review board. After giving informed consent, 23 ASA class III or IV patients, 18-75 years of age, undergoing major cardiovascular, neurosurgical, open heart or abdominal surgery served as the experimental subjects. Premedication included diazepam (0.1-0.15 mg/kg, PO) and atropine (0.4 mg, IM) one hour before operation. All other concurrent medications were continued until the time of surgery. Prior to anesthetic induction a modified V_5 EKG was continuously recorded and catheters were placed in a peripheral vein and radial and pulmonary arteries using standard techniques. Patients were given pancuronium (1.0-1.5 mg, IV), preoxygenated, and randomly selected to receive one of the two induction techniques. Group 1 received fentanyl (300-600 µg/ min, IV) until unconscious and then an additional dose of fentanyl equal to that required for unconsciousness. Group 2 patients received fentanyl (250 µg, IV) followed in 3 minutes by etomidate (0.4 mg/kg, IV) injected over 30-45 seconds. Both groups were given succinylcholine (1.0-1.5 mg/kg, IV) 2 minutes after induction was completed and had their tracheas intubated. Following this, isoflurane (0.5-2.0%) + nitrous oxide (50-60%) and oxygen were administered as clinically indicated. Measurements of heart rate (HR), systolic (SBP) and diastolic (DBP) arterial pressure, central venous pressure (CVP), pulmonary artery systolic (PAS), diastolic (PAD) and wedge pressure (PCWP), and cardiac output (thermodilution) were obtained and cardiac index (CI), systemic (SVR) and pulmonary vascular (PVR) resistances were calculated prior to induction, 2 minutes after fentanyl or fentanyl-etomidate, 1 minute after intubation and every 10 minutes for the first 30 min of anesthesia. Side effects of chest wall rigidity, pain on injection and myoclonus were evaluated during the induction sequence. Data were analyzed utilizing BMDP software (PID, P3D), in particular, T-tests and Hotelling T-square analysis. Statistical significance was considered to be $p < 0.05$.

Results: There were no significant differences between the fentanyl and etomidate-fentanyl groups with respect to age, height, weight, ASA class, or control HR, CI, or PAP. The etomidate-fentan group had a significantly higher SBP at control ($p = 0.02$) (Table 1). During the induction sequence there were no differences between the two groups regarding changes in HR, CI, SBP, or PAP or any other measured or derived variables. Differences in postoperative respiratory depression or nausea and vomiting were not determined. Induction complications included chest wall rigidity (4 of 11 fentanyl patients), pain on injection (1 of 12 fentanyl-etomidate patients) and myoclonus (3 of 12 fentanyl-etomidate patients).

Table 1

Hemodynamic Changes during Induction (mean ± SEM)

		Control	Post Drug	Post Intub	10' Post
HR	F	76 ± 5	74 ± 5	83 ± 5	67 ± 4
(BPM)	E	83 ± 5	75 ± 5	79 ± 5	68 ± 6
SBP	F	128 ± 4	133 ± 6	135 ± 6	112 ± 4
(mmHg)	E	158 ± 11*	136 ± 12	151 ± 12	128 ± 10
CI (L/	F	3.2 ± .4	3.3 ± .5	3.3 ± .4	2.3 ± .3
min/m^2)	E	3.2 ± .3	2.8 ± .3	2.9 ± .2	2.6 ± .3
PAP	F	24 ± 4	28 ± 3	29 ± 3	23 ± 2
(mmHg)	E	22 ± 1	24 ± 1	25 ± 1	22 ± 2

* $p < 0.05$ from fentanyl

Discussion: The results of this study indicate that anesthetic induction with a fentanyl-etomidate combination in patients with poor cardiovascular reserve does not significantly affect hemodynamics during induction or after endotracheal intubation and is associated with a low incidence of easily managed side effects. The data suggest that induction with fentanyl-etomidate may be preferable to high doses of fentanyl in a patients with poor cardiovascular reserve in whom postoperative ventilation is undesirable.

Title: THE EFFECT OF DILTIAZEM ON INTRACRANIAL PRESSURE IN CATS

Authors: S. Thiagarajah, M.D., I. Azar, M.D., E. Lear, M.D.

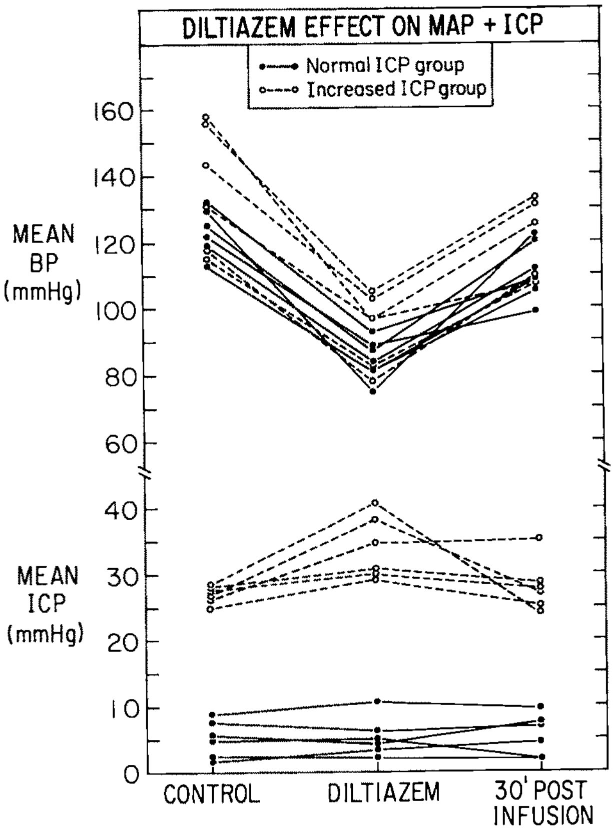
Affiliation: From the Department of Anesthesiology of Beth Israel Medical Center,
Mount Sinai School of Medicine (CUNY), New York, N.Y., 10003

Introduction. The commonly used vasodilators sodium nitroprusside and nitroglycerine increase the intracranial pressure (ICP) and are not recommended for patients with increased ICP. Diltiazem, a calcium channel blocker, possesses vasodilating properties (1) but its effect on ICP has not been reported. This study was designed to determine the effect of diltiazem on normal and increased ICP in cats.

Method. Twelve cats were anesthetized with isoflurane. Their tracheas were intubated and the lungs ventilated with a Harvard animal respirator. A femoral vein was cannulated for drug administration and a femoral artery for blood pressure monitoring and blood gases analysis. The cats were then placed in sphinx position using a steriotactic frame. The scalp and the underlying muscles were dissected and a 5 mm hole was trephined in the left parietal area. A catheter was threaded into the subarachnoid space and connected to a pressure transducer for continuous monitoring of ICP. The cats were then divided into two groups: One with normal ICP (N-ICP) and the other with artificially increased ICP (AI-ICP). In the AI-ICP group a size 10F Foley catheter was placed in the epidural space through a 5 mm trephined hole on the right parietal area. Both trephined holes were sealed with bone wax. After completion of surgery the scalp incisions were infiltrated with 2-3 ml of bupivecaine 0.5% and the isoflurane was discontinued. Anesthesia was maintained with nitrous oxide in 30% oxygen supplemented by intermittent doses of pancuronium. The Foley catheter's balloon in the AI-ICP group was inflated slowly with water until the ICP reached a level of 25-30 mmHg and then remained steady. The blood pressure, heart rate, ICP, EKG, end-tidal CO2 and temperature were continuously monitored. The PaCO2 was maintained at 30+2mmHg and the PaO2 above 100mmHg. Rectal temperature was maintained at 37+0.5 degrees centigrade. After an hour of stabilisation diltiazem infusion, 100-300 µg/Kg/min, was started with an infusion pump. The dose of infusion was adjusted to reduce the blood pressure by 30% for 15 minutes. The highest ICP values, as well as mean blood pressure, heart rate, and EKG before during and for 30 minutes after the diltiazem infusion was discontinued were compared. All measurements were taken at the end of expiration and the zero level for the ICP was referenced to a fixed point at the level of the external auditory meatus. The results were analysed using Student's paired t-test. P values less than 0.05 were considered significant.

Results. The results are summarised in the Figure. Diltiazem produced a dose dependent reduction in mean blood pressure in all cats (from 124+3 mm/Hg to 85+2 mm/Hg and from 134+6 mm/Hg to 94+4 mm/Hg in the N-ICP and AI-ICP groups, respectively; $p<0.005$ for both groups). During the period of hypotension the ICP increased from 5.7+1 mm/Hg to 6.7+1.5 mm/Hg ($P<0.1$) in the N-ICP group and from 26.9+0.5 mm/Hg to 34.0+1.9 mm/Hg ($P<0.004$) in AI-ICP group. Diltiazem reduced the heart rate in both groups (from 223+6 beats/min to 197+8 beats/min in the N-ICP group and from 220+23 beats/min to 182+12 beats/min in the AI-ICP group; $P<0.01$ for both). The electrocardiographic PR interval did not change significantly except in one cat where the PR interval increased from 0.1 to 0.36 msec and remained prolonged at 30 minutes after diltiazem was discontinued. Two cats sustained transient ventricular arrhythmias. No tachyphylaxis occurred during the administration of diltiazem and no rebound hypertension was observed after its discontinuation.

Discussion and Conclusions. Diltiazem is as potent a vasodilator as verapamil, but less potent than nifedipine. It also has negative inotrophic, chronotrophic and dromotrophic effects (1). We observed dose-dependent induced hypotension with diltiazem, but the onset and recovery were slower than those reported with sodium nitroprusside. Diltiazem increased the ICP in both groups, however the increase was significant only in the AI-ICP group (fig 1). Recently diltiazem has been shown to dilate spastic cerebral vessels (2); perhaps this is how diltiazem raises ICP. In patients with increased ICP a further increase in ICP may compromise brain perfusion. We therefore conclude that diltiazem should be used judiciously in patients with increased ICP.



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TITLE: THE PULSE OXIMETER, A NON-INVASIVE MONITOR OF OXYGENATION DURING ONE-LUNG ANESTHESIA

AUTHORS: DM Thys MD, E Cohen MD, JB Eisenkraft MD, JA Kaplan MD

AFFILIATION: Department of Anesthesiology, The Mount Sinai School of Medicine, One Gustave Levy Place, New York City, NY 10029.

INTRODUCTION During one-lung anesthesia (OLA) for lateral thoracotomy, arterial oxygenation is often impaired because of V/Q abnormalities. The degree of intrapulmonary shunting and hypoxia can vary during the course of the procedure and thus continuous monitoring of arterial oxygen tension (PaO_2) is desirable. A pulse oximeter (BTI BIOX III) which utilizes the pulsations of arterial blood flow to modulate the light emitted for the measurement of arterial saturation (SaO_2) has recently become available for clinical use. The aim of this study was to evaluate whether, during thoracic anesthesia, the continuous monitoring of SaO_2 provides a reliable indication of trends in PaO_2.

METHODS After institutional approval and informed consent had been obtained, ten adult patients scheduled for lung resection in the lateral position were studied. Prior to induction of anesthesia, radial artery and thermodilution pulmonary artery catheters were inserted. In addition, a BTI BIOX III Finger probe (Model 117) was placed on the index finger of the non-dependent hand. Arterial saturation and pulse rate were continuously displayed on the oximeter. After induction with thiamylal sodium 3.5 mg/kg and pancuronium 0.15 mg/kg, endobronchial intubation was performed with a Robertshaw double-lumen tube. Anesthesia was maintained with isoflurane 1.0-1.5% (inspired) and N_2O/O_2 (50/50%). Hemodynamic measurements and arterial blood gases were obtained 15 minutes after stabilization had occurred following any change in ventilation pattern. Arterial pO_2 obtained from an arterial blood sample, and arterial saturation obtained by oximetry were compared. A reduction in PaO_2, versus the preceding sample, accompanied by a reduction in SaO_2 was defined as a true positive (TP) and an increase in PaO_2 with an increase in SaO_2 as a true negative (TN). A decrease in PaO_2 followed by an increase in SaO_2 was termed a false negative (FN), while an increase in PaO_2 followed by a decrease in SaO_2 was a false positive (FP). Specificity (TN/TN+FP), sensitivity (TP/TP+FN) and predictability (TP/TP+FP) of the pulse oximeter to detect reductions in PaO_2 were determined. In addition, the correlation between PaO_2 and SaO_2 was evaluated by linear regression analysis.

RESULTS A total of 63 simultaneous measurements of PaO_2 and SaO_2 were obtained. In 42 of these determinations the PaO_2 was in excess of 100 mmHg. Since minimal changes in saturation were observed at elevated PaO_2, these data points were not included in the further analysis. For the remaining data points a sensitivity of 92%, specificity of 75%, and predictability of 85% were calculated. Linear regression analysis of the 21 measurements (PaO_2 40 to 99 mmHg) provides a correlation coefficient of r = 0.84 and a slope of $SaO_2 = 76 + 0.24\ PaO_2$ (see figure). These measurements were obtained over a broad range of physiologic variables: mean cardiac output 4.11 L/min (range 2.29 - 6.13 L/min), mean pH 7.40 (range 7.34 - 7.49), mean pCO_2 38 mmHg (range 32 - 44 mmHg) and mean temperature 34.5°C (range 33.7 - 36°C).

DISCUSSION The accuracy of the pulse oximeter to measure arterial saturation was previously established in healthy volunteers[1] and in patients with respiratory distress.[2] This study demonstrates that the pulse oximeter, an easy-to-use non-invasive device, provides satisfactory information on trends in PaO_2 during one-lung anesthesia. It is evident from the oxygen dissociation curve that large reductions in PaO_2 can produce minor changes in SaO_2 but the pulse oximeter appears sensitive enough to detect those small variations.

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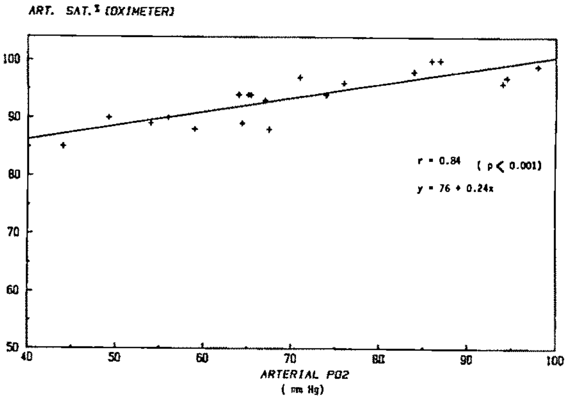

TITLE: EFFECTS OF SODIUM NITROPRUSSIDE ON SYSTEMIC HEMODYNAMICS FOLLOWING CARDIOPULMONARY BYPASS FOR CABG

AUTHORS: D Thys MD, Z Hillel MD, B Mindich MD, M Goldman MD, JA Kaplan MD

AFFILIATION: Departments of Anesthesiology, Surgery and Medicine, The Mount Sinai School of Medicine, One Gustave Levy Place, New York City, NY 10029.

INTRODUCTION In patients with good left-ventricular function, the cardiac index (CI) is markedly elevated in association with a reduction in systemic vascular resistance (SVR) at the end of cardiopulmonary bypass for CABG.[1] As the surgery proceeds, SVR tends to increase, while a reduction in CI is observed. The aim of this study was to investigate whether the administration of sodium nitroprusside (SNP) prevents the increase in afterload and thus maintains cardiac performance.

METHODS After institutional approval and informed consent had been obtained, 20 patients scheduled for three vessel CABG were randomly assigned to a nitroprusside (SNP) treatment or placebo group. The study was conducted in a double-blind fashion. All patients had normal left ventricular function (EF > 50%). After insertion of monitoring lines (radial and pulmonary artery catheters), anesthesia was induced with diazepam 0.5 mg/kg, fentanyl 30 µg/kg and pancuronium 0.15 mg/kg and maintained by infusion of fentanyl 50 µg/kg over 1 hour. A control set of hemodynamic data were obtained after opening of the pericardium. During cardiopulmonary bypass (CPB) all patients were cooled to a core-temperature of 28°C. The treatment infusion (SNP or Placebo) was initiated at the beginning of the rewarming period and maintained until 15 minutes after bypass. The rate of administration was varied to maintain the mean arterial pressure at 50 mmHg while it was attempted to keep the pulmonary capillary wedge pressure between 8-10 mmHg by transfusions from the pump reservoir. The average dose of nitroprusside was 0.8 µg/kg/min. Hemodynamic data were obtained at 5, 10, and 15 minutes after CPB. Data were analyzed using Student's unpaired T-test. All values are expressed as means ± S.E.M.

RESULTS Before cardiopulmonary bypass the hemodynamic performance of both groups did not differ significantly (See Table). After CPB, patients in the nitroprusside group (N) had significantly lower mean arterial pressures (MAP) than patients in the placebo group (P). The cardiac indices (CI) were similar in both groups at 5' but CI in group N exceeded those of group P at 10' and 15' (see figure). Systemic vascular resistances (SVR) were low at 5' in both groups. The infusion of sodium nitroprusside kept SVR low in group N, while it gradually increased in group P. The left ventricular stroke work indices (LVSWI) of group P exceeded those of group N at 5, 10, and 15 minutes. The hematocrit was 23.6% at 5' in both groups and at 15' rose to 25.8% in group N and 26.1% in group P.

DISCUSSION Our findings show that both the systemic vascular resistance and afterload are decreased at the end of CPB. A low hematocrit is the most likely explanation for this as observed by other authors.[1] This experiment however, demonstrates that the administration of sodium nitroprusside maintains a low SVR, while in the placebo group, the SVR rapidly returns to higher values. The low SVR and reduced afterload result in an increase in cardiac index and reduced myocardial work load.

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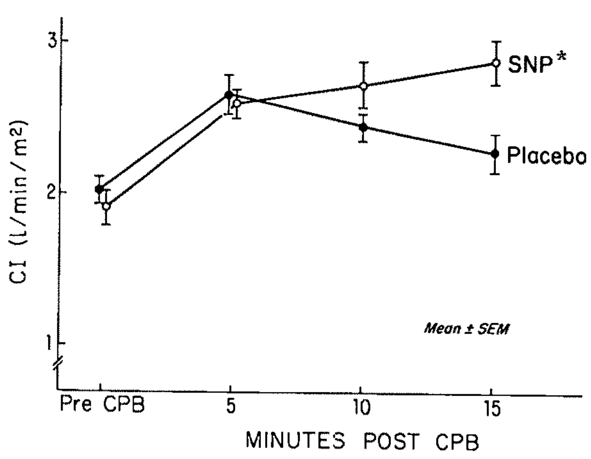
TABLE

Variable		Control	Post CPB	Post CPB	Post CPB
HR	P	62±2.5	79±4.4	78±4.1	76±3.5
	N	56±2.5 NS	75±4.1	76±4.1	78±3.5
MAP	p	83±2.8	60±1.9	67±2.8	68±2.5
	N	75±5.0 NS	48±1.9 †	48±1.3 †	53±2.5 †
PCW	P	8.5±0.8	9.7±0.7	9.7±0.7	8.7±0.7
	N	9.6±1.3 NS	9±0.4	9.1±0.5	9.4±0.4
CI	p	2.01±0.09	2.66±0.19	2.45±0.16	2.28±0.16
	N	1.9±0.16 NS	2.59±0.13	2.75±0.22	2.88±0.22 *
SVR	p	1750±140	951±72	1196±146	1278±88
	N	1813±234 NS	828±83	795±83 *	829±88 #
LVSWI	p	32.3±2.0	26.0±2.2	24.1±2.0	24.8±2.4
	N	31.2±4.4 NS	17.9±1.1 *	19.2±2.0 *	21.6±2.8

* $p < 0.05$ # $p < 0.01$ † $p < 0.001$ (Nitroprusside v. Placebo)
HR = beats/min, MAP & PCW = mmHg, CI = L/min/m^2
SVR = dyn.sec/cm^5 LVSWI = gm.m/m^2



Title: TRANSCUTANEOUS AND LIVER SURFACE PO_2 DURING NORMOTENSIVE SHOCK IN DOGS

Authors: KK Tremper, M.D., SM Hufstedler, M.D., J Zaccari, B.S., V Lee, B.S., D Skinner, M.D., M Weiss, B.S.
B Cross, M.D.

Affiliation: Department of Anesthesiology, University of California Irvine Medical Center, Orange, California

Introduction: Transcutaneous PO_2 ($PtcO_2$) has been demonstrated in expermimental and clinical studies to follow changes in arterial PO_2 (PaO_2) when cardiac index (CI) is adequate and to follow CI during hypotensive low flow shock (1-3). The purpose of this study was to determine the relationship between $PtcO_2$, standard hemodynamics and a central organ PO_2 during hemorrhagic shock and induced normotensive shock.

Methods: Six mongrel dogs were anesthetized with sodium pentobarbital, intubated and mechanically ventilated with room air to an arterial PCO_2 of 40 torr. Arterial and pulmonary artery catheters were placed via a femoral cut down. A $PtcO_2$ electrode, heated to 45°C, was zeroed and calibrated to room air and placed noninvasively on a shaved portion of the chest. A $PtcO_2$ electrode heated to 37°C was similarly calibrated and placed on the liver surface under direct visualization via a sub costal incision. Data sets included heart rate; systemic, pulmonary artery and central venous blood pressures; cardiac output by thermal dilution; arterial and mixed venous blood gases and pH; hemoglobin; $PtcO_2$; liver surface PO_2 (P_LO_2); and mixed venous blood lactic acid level. After the three sets of baseline data were collected, the dogs were progressively hemorrhaged to a mean arterial pressure (MAP) of 40 mm Hg. This MAP was maintained by hemorrhage or transfusion with shed blood. Data sets were collected approximately every 20 minutes for one hour. At this point an infusion of phenylephrine (80 µgm/ml) was titrated to produce a MAP which approximated the baseline MAP. Three data sets were again collected. The phenylephrine infusion was stopped and data were collected after the dogs were resuscitated with the shed blood.

Results: The mean values of some of the hemodynamic and oxygen transport data are presented in the table. $PtcO_2$ and P_LO_2 had significant positive correlations ($r > 0.7$) with each other and with CI. MAP and heart rate were not significantly correlated (r values between 0.50 and -0.5) with CI, $PtcO_2$, P_LO_2 or oxygen delivery. PaO_2 did not change significantly during the study. One of the six dogs died during resuscitation. During the resuscitation of this dog, the P_LO_2 was zero and the $PtcO_2$ averaged 4 torr while the PaO_2 was 110 torr and the lactic acid progressively rose to 16 m mol/l.

Discussion: $PtcO_2$ was initially introduced to neonatal medicine as a noninvasive PaO_2 monitor. Over recent years $PtcO_2$ has been demonstrated to respond as a peripheral tissue PO_2, i.e., it follows PaO_2 when blood flow is adequate and follows cardiac output during shock and resuscitation (1-3). Since $PtcO_2$ is actually a heated skin PO_2, it is of interest to know how this PO_2 compares to the PO_2 of a central vital organ, P_LO_2. $PtcO_2$ followed P_LO_2 closely during shock and resuscitation, Table. It is often difficult to detect low cardiac output clinically when pulse and MAP are normal. During the phenylephrine induced normotension the $PtcO_2$ and P_LO_2 remained low, detecting the low tissue perfusion. The tissues had inadequate O_2 delivery which resulted in reduced oxygen consumption and increasing lactic acid levels, Table. We conclude that $PtcO_2$ follows the trend of tissue PO_2 during shock in spite of normal blood pressure as demonstrated by its correlation with P_LO_2 and CI.

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HEMODYNAMIC AND O_2 TRANSPORT DATA

	Control Data	Hemorrhagic Shock	Normotensive Shock	Post Resuscitation
MAP, mm Hg	105 ± 8	40 ± 4	110 ± 15	126 ±23
CI, L/minM^2	3.6 ± 1.0	0.9 ± 0.3	1.0 ± 0.2	2.9 ± 1.0
O_2 Del i, ml/minM^2	680 ± 230	107 ± 32	106 ± 41	465 ± 241
VO_2 i, ml/minM^2	82 ± 26	67 ± 26	48 ± 31	49 ± 22
Lactic acid, m mol/l	2.8 ± 1.3	8.5 ± 1.0	10.5 ± 2.0	9.0 ± 0.8
P_LO_2, torr	58 ± 11	7 ± 13	6 ± 15	60 ± 14
PaO_2, torr	84 ± 18	83 ± 23	93 ± 27	87 ± 22
$PtcO_2$, torr	83 ± 9	20 ± 22	15 ± 20	56 ± 39
$PtcO_2$, index	1.0 ± 0.2	0.25 ± 0.2	0.2 ± 0.3	0.67 ± 0.5

Data are presented as mean ± standard deviation. MAP = mean arterial pressure; CI = cardiac index; O_2 Del i = oxygen delivery index; VO_2 i = oxygen consumption index; Lactic acid concentration in mixed venous blood; P_LO_2 = liver surface PO_2; PaO_2 = arterial PO_2; $PtcO_2$ = transcutaneous PO_2; $PtcO_2$ index = $PtcO_2/PaO_2$

Title: HEMODYNAMIC EFFECTS OF ATRACURIUM, VECURONIUM AND PANCURONIUM DURING SUFENTANIL ANESTHESIA DURING ELECTIVE CORONARY ARTERY SURGERY

Authors: CS Waldmann, FFARCS, KJ Wark, FFARCS, PS Sebel PhD, FFARCSI and *RO Feneck, FFARCS
Affiliation: Anaesthetics Unit, London Hospital Medical College, Whitechapel, London E1 1BB and *Anaesthetics Department, London Chest Hospital, Bonner Road, London E2

INTRODUCTION

Pancuronium has been extensively used as a neuromuscular blocking agent during high dose opioid anesthesia for cardiac surgery. This is because its positive chronotropic action offsets opioid induced bradycardia. This study was undertaken to compare the cardiovascular effects of atracurium (A) and vecuronium (V) with pancuronium (P) during sufentanil anesthesia.

METHOD

Following local institutional ethical committee approval, 30 consenting adults scheduled for elective coronary artery surgery were randomly allocated into 3 equal groups, P, V and A. After premedication with a benzodiazepine, papaveretum 15-20mg and hyoscine 0.3-0.4mg and one-third the daily dose of beta blocker, a radial artery catheter, flow directed pulmonary artery catheter and intravenous cannula were inserted under local analgesia. ECG and neuromuscular transmission monitor (Organon Tecknika) were attached. The cardiovascular monitor used was a Kone 565A connected to an Apple microcomputer and minute mean values for the cardiovascular variables were recorded automatically. Following administration of 0.05mg/kg P, 0.05mg/kg V or 0.3mg/kg A, anesthesia was induced with sufentanil 15µg/kg, followed by a repeated dose of neuromuscular blocking agent. Ventilation was with 100% O_2. Supplements of P, 0.05mg/kg or a variable rate infusion of A or V were used to ensure less than 10% neuromuscular transmission. Sufentanil 5-10µg/kg was given before sternotomy. Atropine was given if the instantaneously recorded heart rate was less than 40 beats/min. Nitroglycerin was used to control hypertension and metaraminol for hypotension. Data are presented as mean ± SD. Statistical analysis was by repeated measures ANOVA (BMDP2V).

RESULTS

Statistical analysis was performed on the following data points; control, induction +2 min, intubation +1, +2, +3, +4, +5, pre incision, incision +2, +5 and sternotomy +2, +5. Cardiac output measurements were taken before induction, induction +2, intubation +2, incision +2, sternotomy +2. There were no statistically significant differences between the 3 groups for any of the measured or derived cardiovascular parameters. Atropine was required by 2 A, 1 V and 0 P patients. Two patients in A and P groups and 1 in the V group developed hypertensive episodes at sternotomy. These patients were treated successfully with nitroglycerine. One A patient required methoxamine 1mg before skin incision.

DISCUSSION

The cardiovascular effects of sufentanil seen in this study are broadly comparable with those described by other workers (1). Significant tachycardias were not seen after P, probably as a result of pre-treatment with beta blockers. Even though hypertension at sternotomy may be slightly less common with atracurium and vecuronium, bradycardias occur at induction with these relaxants. For this reason, the new generation muscle relaxants did not appear to offer any major advantage over pancuronium for this technique of anaesthesia.

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TABLE

Heart Rate Beat/Min

	CONT	IND+2	INT+2	INC+2	STERN+2
P	55.7	63.4	64.3	69.1	59.3
	±9.0	±11.7	±9.0	±25.2	±6.9
V	60.3	56.9	59.0	49.1	56.7
	±10.8	±12.1	±11.4	±6.2	±10.5
A	61	55.9	62.0	54.6	55.4
	±10.7	±17.3	±15.7	±16.9	±10.3

Mean Arterial Pressure mm Hg

	CONT	IND+2	INT+2	INC+2	STERN+2
P	87.3	72.8	76.9	77.8	91.7
	±14.9	±14	±10.2	±16.9	±14.3
V	83.7	72.5	81.3	78.5	88.7
	±11.5	±14.1	±12.8	±8.0	±12.6
A	92.4	64.2	78.6	84.6	99.3
	±17.5	±15.8	±14.9	±15.5	±21.6

Cardiac Index l/min/m^2

	CONT	IND+2	INT+2	INC+2	STERN+2
P	2.7	2.9	3.2	2.3	2.1
	±0.4	±0.6	±0.9	±0.5	±0.3
V	2.5	2.8	2.6	2.0	2.0
	±0.4	±0.4	±0.4	±0.4	±0.1
A	2.7	2.8	2.8	2.1	2.4
	±0.4	±0.4	±0.5	±0.2	±0.6

Title: THE EFFECT OF PH ON SUBARACHNOID BLOCKADE WITH SODIUM METABISULFITE IN RABBIT

Authors: B.C. Wang, M.D., D.E. Hillman, Ph.D., H. Turndorf, M.D.

Affiliation: Departments of Anesthesiology and Physiology, New York University Medical Center,
550 First Avenue, New York, N.Y. 10016

Introduction: Sodium bisulfite (SBS), acetone sodium bisulfite and sodium metabisulfite (SMBS) produce chronic block when introduced into the subarachnoid space (SAS) of rabbits.[1,2,3] In addition, 0.2% SBS depresses neuronal conduction of the vagus nerve.[4] The vagal depressant effect can be modified by changes in pH.[4] There is no data available to determine whether changes of pH will modify the blocking action of these drugs in the SAS. The present study investigates the effect of pH adjustment on the subarachnoid block of SMBS.

Method: Under N_2O + O_2 and halothane endotracheal anesthesia, a PE 10 catheter was aseptically inserted through lumbar laminectomy and directed caudally in the (SAS) of 3-4 Kg New Zealand albino rabbits. Twenty-four hours after surgery, all animals were tested for sensory, motor and sphincteric functions. Only those without perceptible impairment were divided into four groups, receiving in the awake state, control solutions (NS & RL) and 0.2% SMBS in Ringers Lactate (RL) at pH 5.2, 7.2, or 7.5 (adjusted c̄ NaOH). A preliminary test spinal block with 1-2 mg of 2-chloroprocaine was used to confirm the correct position of the implanted catheter. Following recovery from the test block, control and test solutions were injected through the catheter via a 0.22 μ filter.

Group I Control: 6 animals received 0.5 ml of RL pH 6.1, Mos 272 and 6 animals received 0.5 ml of normal saline pH 5, Mos 308.

Group II: 7 animals received a single dose of 1.2 mg of SMBS (0.6 ml of 0.2% solution in RL) pH 5.2, Mos 283. A second 1.2 mg dose was given in two rabbits because there was no apparent response to the initial injection.

Group III: 7 rabbits received 1.2 mg (0.6 ml) of 0.2% SMBS pH 7.2, Mos 272.

Group IV: 6 rabbits received 0.6-1.2 mg (0.3-0.6 ml) of 0.2% SMBS pH 7.5, Mos 296.

Results: Group I: No Neurologic changes were seen with either RL or NS.

Group II: All animals developed hind limb paralysis (HLP) within 35 minutes to 24 hours following one or two doses of subarachnoid SMBS. Four animals paralyzed after receiving 1.2 mg of subarachnoid SMBS recovered: one in 2 hours, one in 3 days, one in 8 days, and one in 12 days. After sustaining HLP for 5 and 18 days two animals were sacrificed by perfusion under anesthesia for pathological examination of the spinal cord. Two died spontaneously after 1.2 mgs of SMBS - one at 3 days, another at 10 days. Both had partial HLP with the former also having fecal and urinary incontinence. A third with chronic HLP died 12 days after receiving 2.4 mg of SMBS.

Group III (pH 7.2): One rabbit developed persistent HLP after receiving 1.2 mg of SMBS and was perfused for pathological examination one week later. Four rabbits developed HLP after receiving 1.2 mg of SMBS and recovered in 4 days, 2 days, 2 hours 25 minutes and 65 minutes respectively. The remaining two rabbits did not develop HLP. Group IV (pH 7.5): One rabbit developed HLP after receiving 0.6 mg of SMBS, persisting for 3 weeks. A second rabbit developed transient urinary incontinence without HLP after 0.6 mg of SMBS and recovered in one day. This animal was examined pathologically. A third rabbit, after receiving 1.2 mg of SMBS developed paralysis of tail movement associated with urinary and rectal incontinence. This persisted for one week and finally recovered. There was no HLP. A fourth rabbit died spontaneously two hours after receiving 1.2 mg of SMBS. The remaining 2 rabbits did not show any HLP or sphincteric incontinence after receiving 1.2 mg of SMBS. The following table summarizes the results.

SAS INJECTION	NS pH 5 (n6)	RL pH 6.1 (n6)	SMBS pH 5.2 (n7)	SMBS pH 7.2 (n7)	SMBS pH 7.5 (n6)
HLP c̄ INC	0	0	7(100%)	5(70%)	1(16%)
TAIL P INC S̄ HLP	0	0	0	0	1
URINARY INC S̄ HLP	0	0	0	0	1
RECOVERY OF HLP OR INC	NA	NA	4/7 (57%)	4/5 (80%)	2/3 (66%)
NO APPARENT EFFECT	6	6	0	2	2
DEATH	0	0	3	0	1

SAS-Subarachnoid Space; HLP-Hind Limb Paralysis; SMBS-Sodium Metabisulfite; RL-Ringer's Lactate; NS-Normal Saline; NA-Not Applicable; INC-incontinence; P-paralysis.

Discussion: In an isolated desheathed rabbit vagus nerve study, Gissen (4) et al showed irreversible conduction block by bisulfite at a pH below 5 and no block at pH above 7. Our result is in general agreement with that of Gissen et al except we did encounter block above pH of 7 using the same concentration of 0.2% as that by Gissen. The discrepancy here may suggest that the direct action of bisulfite is more pronounced in the SAS *in vivo* than on isolated nerve *in vitro*. This study suggests that the subarachnoid blocking action of SMBS is attenuated but not completely abolished by increasing the pH from 5.2 (Group II) to 7.2 (Group III) and 7.5 (Group IV). All animals in group II developed HLP, 5 out of 7 (70%) in Group III had HLP, while 3 out of 6 (50%) in Group IV were neurologically affected; one with HLP, one with paralysis of the tail for 9 days and the other one with incontinence but no HLP. The effect of pH on the blocking action of bisulfite is probably through alteration of the existing pH dependent equilibrium between bisulfite and sulfite. As pH increases, bisulfite decreases and sulfite increases. Bisulfite, not sulfite is the cause of the block.

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Title: NONINVASIVE DETECTION OF ISCHEMIC VENTRICULAR DYSFUNCTION BY CARDIOKYMOGRAPHY IN PATIENTS UNDERGOING ABDOMINAL AORTIC SURGERY

Authors: FI Weitz, M.D.; AJ Berry, M.D.; RB Smith III, M.D.; JH Levy, M.D.
Affiliation: Department of Anesthesiology; Emory University School of Medicine; Atlanta, Georgia 30322

INTRODUCTION Patients with peripheral vascular disease have a high incidence of coronary artery disease. Due to the increased risk of intraoperative myocardial ischemia,[1] patients undergoing abdominal aortic surgery (AAS) at our institution are routinely monitored by inferior and lateral ECG leads as well as intra-arterial and pulmonary artery pressure determination. However, changes in these are late indications of myocardial ischemia and it is desirable to have a more sensitive monitor. The cardiokymograph (CKG) is a *noninvasive* electromagnetic sensing device capable of assessing left ventricular anterior wall motion,[2] the earliest indicator of myocardial ischemia.[3] This monitor has been used to assess left ventricular ischemia in patients undergoing CABG.[4] The purpose of our study was to evaluate the CKG (Cardiokinetics, Inc.; Bellevue, WA) as a monitor of left ventricular dysfunction during AAS.

METHODS With institutional approval and informed consent from each patient, we studied all adult patients undergoing AAS by one surgeon over a three month period. Patients were anesthetized with either fentanyl, a halogenated inhalation agent, or a combination of these agents. Patients were monitored using ECG leads II and V_5, radial and pulmonary artery catheters, and CKG continuously recorded on a multi-channeled strip chart recorder. All measurements were routinely recorded before and after induction of anesthesia, after intubation, and before and after aortic clamping and declamping. Fluids and vasodilators (NTG, SNP) were given to maintain normal systemic and pulmonary capillary wedge pressures to normalize cardiac output. Nitroglycerin was administered to all patients prior to applying the aortic cross clamp.

RESULTS Seven patients (range 52-79 years; 5 ASA class III & 2 class IV) were included for study. Abnormal left ventricular anterior wall motion was observed in only one patient during intubation (Fig. 1,2) without ECG or hemodynamic evidence of myocardial ischemia. These changes (Table) resolved within 10 minutes. No patient exhibited ECG, CKG or hemodynamic ischemic changes during aortic clamping or unclamping.

DISCUSSION CKG has been shown to be a sensitive detector of left ventricular ischemia.[2] The lack of CKG, ECG or hemodynamic changes with aortic cross-clamping might be explained by the aggressive hemodynamic control routinely used during these procedures. The abnormal wall motion seen on intubation of one patient in the absence of ECG or hemodynamic changes probably revealed regional ischemia which would have otherwise gone undetected. The noninvasive and inexpensive nature of CKG combined with its ability to detect left ventricular wall motion abnormality make this a promising monitor for the operative setting.

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TABLE
Hemodynamics in 1 patient with abnormal CKG

	Induction	Intubation	2 Min $\bar{p}$ Intubation*
BP	120/65	180/120	145/85
PA	30/14	36/22	22/14
Pulse	60	85	90

*Time of abnormal CKG

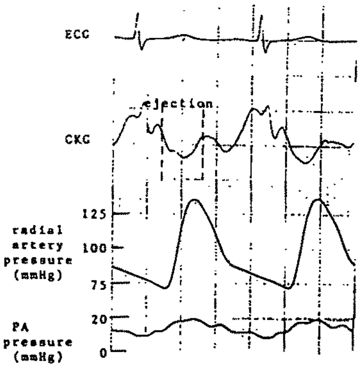

Fig 1

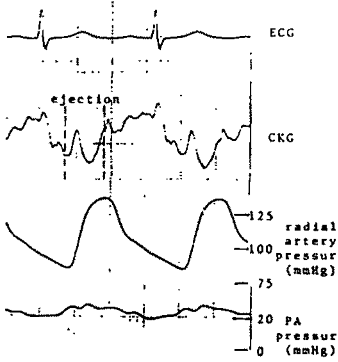

Fig 2

ECG, CKG, radial artery and PA pressure from the patient that demonstrated an abnormal CKG during intubation. CKG is normal pre-op. (Fig. 1) Note abnormal systolic wall motion during ejection. (Fig. 2)

TITLE: SINGLE VERSUS DIVIDED DOSES OF ATRACURIUM: DOES 0.05 + 0.10 EQUAL 0.15?

AUTHORS: G. Weinberg, M.D., J.A. Stirt, M.D., and D. E. Longnecker, M.D.

AFFILIATION: Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, VA 22908

Introduction. Use of a small dose of atracurium shortly before a larger dose has been reported to speed the onset of suitable intubating conditions as well as decrease the total dose requried for intubation (1). Also, neuromuscular block (NMB) has been shown to occur more rapidly when atracurium 0.5 mg/kg is given in divided doses rather than by single bolus injection (2). In apparent contradiction to these reports, NMB after a single bolus of 0.25 mg/kg of atracurium was found to be greater than that following the same dose given in increments (3). Our study was designed to determine if the combined effect on NMB of pretreatment with a small (subclinical) dose of atracurium followed by a second (therapeutic) dose differs from a single bolus injection.

Methods. Institutional approval and informed consent were obtained. Studies were completed on 20 adult patients, ASA class 1 or 2. No premedication was given. Anesthesia was induced with thiopental 4-6 mg/kg and maintained with fentanyl 3-5 µg/kg and N_2O, 67%, in O_2. The ulnar nerve was stimulated supramaximally at 0.15 Hz, and force of thumb adduction was measured with a force tranducer and recorded. Patients were randomly allocated into either Group 1 (atracurium 0.15 mg/kg) or Group 2 (atracurium 0.05 mg/kg followed 5 minutes later by 0.10 mg/kg), and atracurium was administered. Maximal NMB, time to initial twitch depression, and time to maximal NMB were measured, as were times to 25, 50, and 95% recovery of initial twitch height. Student's t-test was used to test statistical significance, with $p<0.05$ considered significant.

Results. Maximal NMB, time to initial twitch depression, and time to maximal NMB for both dose regimens are shown in Table 1. Maximal NMB and the time required to achieve maximal NMB were the same whether atracurium 0.15 mg/kg was delivered in a single bolus or by divided dose. A statistically significant difference was found for the time to initial twitch depression. Thus, pretreatment decreased by 30 seconds the time to a measurable effect of the second dose on twitch height. The times required for recovery of neuromuscular function (Table 2) were not statistically different between Groups 1 and 2.

Discussion. For the total dose examined (0.15 mg/kg), pretreatment with a clinically undetectable dose of atracurium does not appear to affect the intensity of NMB, time to maximal NMB, or recovery from NMB. However, a trend toward slightly increased duration for recovery from NMB was clinically evident. The initial blockade following the combined dose occured slightly sooner than with a single dose. An earlier study (2) documents a similar effect for a total atracurium dose of 0.5 mg/kg. This dose is in excess of the ED95 of atracurium (4) and produces a blockade that diminishes the ability to discriminate subtle alterations in drug effect. The maximal NMB achieved in our study with 0.15 mg/kg is in agreement with previously reported values for the ED75 of atracurium (4), and such a degree of NMB provides a sensitive way of assessing the affects of a cumulative dose regimen. Recently, the "priming principle" has been formulated to describe use of a small dose of atracurium shortly before a larger dose to speed the onset of, as well as decrease the total relaxant dose required for, adequate intubating conditions (1). Our results show a more rapid onset of initial twitch depression following a divided dose regimen, but maximal NMB and time to maximal NMB do not appear to differ whether atracurium is administered in single or divided doses.

Table 1

Atracurium dose (mg/kg)	Maximal neuromuscular block (%)	Time to initial twitch height depression (min)	Time to maximal neuromuscular block (min)
0.15	73±7	1.6±0.2	7.3±0.5
0.05**+0.10	74±7	1.1±0.2*	7.6±0.9

Values are mean±SEM; * = $p<0.05$
NMB did not occur in any patient following 0.05 mg/kg dose

Table 2

Atracurium dose (mg/kg)	Time (min) to % recovery from neuromuscular block		
	25%	50%	95%
0.15	18±2	24±4	30±2
0.05+0.10	22±4	26±4	34±2

Values are mean±SEM

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TITLE: USE OF OPIATE INFUSIONS IN ANESTHESIA - DETERMINING OPTIMAL DOSES AND SERUM CONCENTRATIONS

AUTHORS: Paul F. White, Ph.D., M.D., Man-Ling Sung, M.S.

AFFILIATION: Department of Anesthesia, Stanford University School of Medicine, Stanford, CA 94305

INTRODUCTION: Opiate analgesics are commonly administered as incremental bolus doses during general anesthesia. Recent studies (1,2) have demonstrated that continuous infusions of intravenous (IV) analgesics significantly decreases the drug dosage requirement, improves intraoperative conditions, and decreases recovery time compared with traditional intermittent bolus techniques. The objective of this study was to determine the optimal maintenance infusion rate for morphine, meperidine, or fentanyl when used during general anesthesia with nitrous oxide and muscle relaxants. The minimum effective (analgesic) concentrations during surgery were determined for the three commonly used opiate compounds.

METHODS: Ninety, consenting, ASA physical status I or II patients undergoing elective general surgical procedures were randomly assigned to receive either morphine sulfate (MS), meperidine (M), or fentanyl (F). The study was approved by the local Institutional Review Board. All patients were premedicated with diazepam, 0.2 mg/kg p.o. Patients assigned to the morphine group, received one of three loading doses (LD)-maintenance infusion rates (MIR), namely 0.1 mg/kg - 1.5 µg/kg/min, 0.2 mg/kg - 3 µg/kg/min, or 0.3 mg/kg - 4.5 µg/kg/min. The LD-MIR regimens for meperidine consisted of 1 mg/kg - 15 µg/kg/min, 2 mg/kg - 30 µg/kg/min, or 3 mg/kg - 45 µg/kg/min. The LD-MIR regimens for fentanyl were 3 µg/kg - 0.03 µg/kg/min, 6 µg/kg - 0.06 µg/kg/min, or 9 µg/kg - 0.09 µg/kg/min. The LD was administered 3-5 min prior to induction of anesthesia with thiopental 2 mg/kg and succinylcholine 1.5 mg/kg. The induction was described as adequate if the patient was unconscious and the mean arterial pressure (MAP) and heart rate (HR) remained within ±25% of the baseline values during intubation. If the induction was inadequate, additional bolus doses of thiopental, 50-100 mg were administered. Maintenance anesthesia consisted of an opiate infusion, nitrous oxide 70% in oxygen, and pancuronium 0.1-0.2 mg/kg. The initial MIR was described as adequate if the MAP and HR remained within ±25% of the preinduction values following skin incision. If signs of inadequate analgesia are noted (e.g., hypertension, diaphoresis, lacrimation, tachycardia), small bolus doses of the opiate (e.g., MS 1 mg, M 10 mg, F 25 µg) were administered and the maintenance infusion rate was increased by 50-100%. If the signs of inadequate analgesia persisted, isoflurane, 0.25-0.5%, was administered. In cases where the MIR appeared to be adequate, it was decreased by 50-100% at 30-60 min intervals until clinical signs of inadequate analgesia were noted. Serum samples were obtained at 5-30 min intervals and analyzed using HPLC (MS), GLC (M), or RIA (F). The minimum effective opiate concentration was determined by averaging the serum drug concentrations at the highest "inadequate" MIR and the lowest "adequate" MIR during the surgical procedure.

RESULTS: The three analgesic groups were similar with respect to demographic characteristics (e.g., age, sex, weight, type and duration of operation). The overall opiate infusion rates (mean values ±SD) for morphine, meperidine, and fentanyl were 0.20±0.06 mg/min, 1.51±0.58 mg/min, and 3.1±1.0 µg/min, respectively. The average infusion rates for the individual LD-MIR groups are summarized in table 1. In all three opiate groups, a significantly higher percentage of patients receiving the lowest LD manifested hemodynamic responses to intubation and skin incision (MAP or HR increased greater than 25% above baseline values) than in the high LD groups. In the morphine group, 40% required low-dose isoflurane to control hemodynamic responses during surgery and 20% required a narcotic antagonist to reverse postoperative respiratory depression. In the meperidine group, 50% required isoflurane and 16% required an opiate antagonist. In the fentanyl group, 30% required isoflurane while none required opiate antagonist. The minimum effective analgesic concentrations for morphine, meperidine, and fentanyl were 113±27, 1192±249, and 3.3±1.6 ng/ml, respectively.

DISCUSSION: Opiate infusions are useful adjuvants during general anesthesia. In this preliminary dose-ranging study, we have established guidelines for the use of morphine, meperidine, and fentanyl infusions during general surgical procedures. When fentanyl was used, there was a decreased requirement for supplementation with volatile anesthetics and fewer patients required opiate antagonists to reverse residual narcotic effect compared to morphine or meperidine. The improved "controllability" with fentanyl may be related to its high lipid solubility. These data would suggest that the enhanced lipophilicity of the new fentanyl analog, sufentanil, might make it an even better analgesic for continuous infusion. Finally, this investigational model may be useful for studying the effects of age, disease states, and other drugs on the narcotic analgesic requirement.

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Table 1: Opiate LD and average MIR values (means±SD)

Morphine sulfate	N	LD (mg/kg)	Avg MIR (mg/min)
Low LD	7	0.11±0.01	0.17±0.07
Medium LD	6	0.22±0.02	0.22±0.05
High LD	6	0.30±0.02	0.23±0.05

Meperidine	N	LD (mg/kg)	Avg MIR (mg/min)
Low LD	7	1.1±0.1	1.8±0.5
Medium LD	8	2.1±0.2	1.4±0.5
High LD	8	3.4±0.7	1.5±0.7

Fentanyl	N	LD (µg/kg)	Avg MIR (µg/min)
Low LD	7	3.2±0.6	2.8±0.8
Medium LD	6	6.3±1.3	3.9±1.0
High LD	6	9.6±0.2	2.6±0.7

Title: HEMODYNAMICS, CARDIAC FUNCTION, OXYGEN USE AND CATECHOLAMINES DURING PORCINE MALIGNANT HYPERTHERMIA

Authors: CH Williams, Ph.D., W Buzello, M.D., SE Dozier, B.S., P Chandra, M.D.,
and CW Gehrke, Ph.D.*, KO Gerhardt, Dr. Sci. Nat.*, JK Wong, B.S.*
Affiliation: Texas Tech University Health Sciences Center, Departments of Anesthesiology and Biochemistry,
El Paso, Tx 79905, and *University of Missouri, Department of Biochemistry, Columbia, Mo 65211

Introduction. Malignant Hyperthermia (MH) is a highly lethal syndrome triggered by inhalational anesthetics and depolarizing muscle relaxants. Our previous studies with the inbred MH susceptible pig model provided evidence that an intense peripheral vasoconstriction, hypermetabolism, and increased blood plasma levels of norepinephrine were key components of the MH syndrome. With the advent of the electrochemical detector for quantitating catecholamines and a highly instrumented recording system for monitoring the pathophysiological changes in MH susceptible pigs we decided to reexamine the initial MH events triggered by halothane.

Methods. Eight Malignant Hyperthermia susceptible outcross pigs (MH x Normal) were studied. Anesthesia was induced and maintained with thiopental (22mg/kg). Invasive monitoring was established by surgical cutdowns to the femoral artery and femoral vein and inserting Swan Ganz and Opticath* catheters. AP, PAP_w, PAP_m, cardiac output by thermodilution, continuous arterial and venous O_2 saturation, core and rectal temperature, heart rate, end tidal CO_2, ECG, and muscle twitch tension were recorded. Arterial and venous plasma samples were collected and processed for catecholamine analysis. The samples were analyzed for norepinephrine and epinephrine levels by (LC-4B) electrochemical detection at 0.65 V, 2 nA full scale after High Performance Liquid Chromatography separation on a Supelcosil LC-18-DB, 150 mm x 4.6 mm column with a mobile phase of 0.025 M citric acid, 0.025 M Na_2HPO_4, $5x10^{-5}$ M EDTA, 35 mg Octyl Sodium Sulfate/L, 3% MeOH, pH 3.5 at a flow rate of 1.2 ml/min. Dihydroxybenzylamine was the internal standard. Each animal served as its own control.

Results. Heart rate increased significantly ($p < .05$) (145 - 192 bpm) five minutes before any other recorded symptom of impending MH. Total peripheral resistance decreased from 1625 to 762 dynes·sec/ cm^5 as the full blown MH syndrome developed. Pulmonary vascular resistance increased from 164 to 225 dyns·sec/cm^5 at the tachycardia stage and remained elevated over control values throughout MH. Pulmonary edema occurred in two pigs. Left ventricular stroke work index dropped significantly from 1.25 to .32 gm·M/Kg/beat at halothane administration, increased to .44 gm·m/kg/beat at tachycardia and peaked at 1.0 gm·M/kg/beat at MH then decreased to .37 gm·M/kg/beat at MH +. Right ventricular stroke work index did not change significantly. Stroke volume index dropped from .85 to .50 ml/beat·Kg at halothane administration, increased to .58 ml/beat·Kg at tachycardia, to .59 ml/beat·Kg at MH then decreased to .52 ml/beat·Kg at MH +. Cardiac index decreased from 108.75 to 79 ml blood flow /min·Kg at halothane administration then increased to 108 ml/min·Kg at tachycardia and 117.5 ml/min·Kg at MH with no further increase at MH +. Oxygen utilization increased from 2.8 to 11.37 ml O_2/min·Kg in a linear curve as the MH syndrome developed. Arterial O_2 saturation could be maintained at 98% during the MH syndrome. However venous O_2 saturation decreased at a rate of 9.0%/min and 5.3%/min in two pigs and at 0.8% min in a third pig. Core temperature increased at a rate of 0.09°C/min.

Norepinephrine plasma levels were 0.36 ng/ml during the control period and increased to 20.79 ng/ml at tachycardia and further increased to 40.58 ng/ml at MH and decreased to 22.02 and 3.29 ng/ml at MH +. Up to 108 ng/ml of norepinephrine were recorded in one pig during MH. Epinephrine plasma levels were 0.30 ng/ml during the control period and increased to 4.9 ng/ml at tachycardia, 18.25 ng/ml at MH and 24.40 ng/ml at MH +. The ratio of norepinephrine to epinephrine was 4.23:1 at tachycardia.

Conclusions. Tachycardia is the first external physiological symptom of impending MH and occurs five minutes before any other signal.

Outcross MH pigs exhibit a decreased peripheral resistance in contrast to our inbred animals which exhibited an increased peripheral resistance.

The high norepinephrine levels are probably activating and opening calcium channels as part of the hormonal stimulus for heat production in muscle. The increase of norepinephrine 3 fold produces tachycardia without MH. However a 10 to 100 fold increase of norepinephrine caused MH with or without rigor and higher levels (up to 300 fold) caused MH with muscle rigor. Other organ systems, i.e. heart and peripheral vascular system are also affected by the MH genetic defect.

The massive release of norepinephrine which initiates tachycardia is playing a key role in accelerating metabolism and initiating the development of MH.

Venous O_2 saturation reflects the most accurate internal indicator of impending MH. Several pigs showed a low rate of O_2 utilization and required an hour or more of halothane exposure to develop MH. Other pigs developed MH after four minutes of halothane.

The metabolic rate during MH exceeds the availability of O_2 delivery and therefore tissues become hypoxic and produce lactic acid.

The increased pulmonary vascular resistance we observed in MH susceptible pigs indicates that pulmonary edema could be an important component of MH in man.

Two pigs developed MH to 45°C without muscle rigor.

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*Oximetric, Inc Mountain View, C

Title: PORCINE MALIGNANT HYPERTHERMIA: TESTING OF ATRACURIUM IN MH SUSCEPTIBLE PIGS

Authors: C.H. Williams, Ph.D., S. E. Dozier, B.S., W.K. Ilias, M.D., and R. T. Fulfer, M. D.

Affiliation: Departments of Anesthesiology and Biochemistry Texas Tech University Health Sciences Center,
El Paso, Texas 79905

Malignant Hyperthermia in man and susceptible pigs can be induced with halothane or other halogenated anethetics and depolarizing muscle relaxants such as succinylcholine. The nondepolarizing muscle relaxants such as Pancuronium, Metubine Iodide, and Vecuronium have been reported to be non-triggering agents for Malignant Hyperthermia (1-3). A previous report of Atracurium testing in two MH susceptible pigs indicated that Atracurium did not trigger MH (4). The purpose of this study was to evaluate the triggering potential of Atracurium in six MH susceptible pigs.

Methods and Materials:

Six Malignant Hyperthermia susceptible pigs from our inbred colony were tested at 8-10 weeks of age with halothane, used for the one hour Atracurium infusion experiment, and then challenged later with halothane during surgery and invasive monitoring for other experiments (see Table I). Anesthesia was induced by intraperitoneal injection of thiopental (33 mg/Kg) and intravenous thiopental was given as needed to maintain anesthesia. Animal weights ranged from 31 to 79 Kg. After intubation the animals were mechanically ventilated at a rate to give an end tidal CO_2 value of 42 torr at 760 torr barometric pressure. The left rear leg was immobilized in a cast and the peroneal nerve was supramaximally stimulated with a train of four every 15 seconds via needle electrodes with an HSE Neurostim. The muscle twitch response was recorded via a Grass FT-10 force displacement transducer connected to a Hewlett-Packard Model 7758 B 8-Channel recorder. Heart rate, ECG, rectal temperature and end tidal CO_2 via a Cavitron CO_2 analyzer were recorded. Atracurium was infused via the ear vein at a rate sufficient to maintain a 90% blocking dose.

Results:

Table I presents the results of the halothane challenge at 8-10 weeks and later during invasive monitoring.

TABLE I

Pig #	Halothane Challenge	Surgical Halothane Challenge
0 - 0	+	+
2 - 3	+	+
3-5	-	N.T.
2-1	+	+
6-0	-	+
1-5	+	N.T.

A mean dose of 0.95 mg/Kg of atracurium produced a 100% neuromuscular blockade (Table II). A dose of 4.0 mg/Kg/hr. of Atracurium was required to maintain a 90% blocking dose during the 60 minute infusion period, and the mean recovery time (25% - 75%) was 10.2 min.

Table III presents the heart rate (HR) rectal temperature and end tidal CO_2 values observed during the Atracurium infusion for each pig. The mean heart rate increased from 142 to 170 bpm. This change was statistically significant at the $P < .08$ level. Rectal temperature decreased from 36.4° to 35.6°. End tidal CO_2 remained steady at 41-42 torr during the experiment.

Atracurium Infusion

Table II

Pig #	Avg Infusion 60 min dose	100% Blocking dose	recovery (25-75)
1-5	3.31 mg/kg-hr	0.95 mg/kg	11 min
2-3	5.34 mg/kg-hr	1.03 mg/kg	8 min
3-5	3.98 mg/kg-hr	0.69 mg/kg	12 min
2-1	3.92 mg/kg-hr	0.97 mg/kg	11.5 min
6-0	3.23 mg/kg-hr	1.02 mg/kg	8.5 min
0-0	4.34 mg/kg-hr	1.02 mg/kg	10.5 min
Mean	4.02 mg/kg-hr	0.95 mg/kg	10.25 min
S.D.	.77 mg/kg-hr	0.13 mg/kg	1.6 min
SEM	0.31 mg/kg-hr	0.05 mg/kg	0.65 min

Atracurium Infusion

Table III

		0 min	10 min	20 min	30 min	40 min	50 min	60 min
1-5	HR	171	175	179	175	159	153	175
	Temp	37.1°C	36.9°C	36.8°C	36.6°C	36.5°C	36.4°C	36.3°C
	CO_2	42	42	41	41	41	41	41
2-3	HR	142	157	159	181	199	193	192
	Temp	36.3°C	36.2°C	36.1°C	36.0°C	35.9	35.7°C	35.6
	CO_2	43	43	42	41	41	40	40
3-5	HR	135	139	148	156	161	135	181
	Temp	35.5°C	35.4°C	35.3°C	35.2°C	35.0°C	34.8°C	34.7°C
	CO_2	40	40	40	40	39	39	39
2-1	HR	179	181	182	191	200	206	208
	Temp	35.4°C	35.3°C	35.2°C	35.1°C	35.0°C	34.8°C	34.6°C
	CO_2	42	42	42	43	43	44	46
6-0	HR	92	92	103	123	118	115	125
	Temp	36.6°C	36.4°C	36.3°C	36.1°C	36.0°C	35.9°C	35.8°C
	CO_2	40	40	39	39	39	38	38
0-0	HR	136	131	128	135	136	141	139
	Temp	37.2°C	37.0°C	27.0°C	36.9°C	36.9°C	36.8°C	35.8°C
	CO_2	44	44	43	42	41	41	41
MEAN	HR	142	146	150	160	162	157	170
	Temp	36.4	36.2	36.1	36.0	35.9	35.7	35.6
	CO_2	42	42	41	41	41	41	41
S.D.	HR	31	33	30	27	33	35	32
	Temp	0.8	0.7	0.7	0.7	0.8	0.8	0.9
	CO_2	1.6	1.6	1.5	1.4	1.5	2.1	2.4

HR = beats per min
Temp = rectal temperature
CO_2 = Torr of CO_2 in expired air corrected to standard pressure

Discussion:

Our previous experimental work with non-depolarizing muscle relaxants indicated that they should not trigger or induce Malignant Hyperthermia, however, we believe it is necessary to test each new drug individually since the precise mechanism of how MH is initiated is not known. We know that stress factors in general, i.e. heat, exercise, fear, pain, may trigger MH in susceptible animals. Therefore drugs which may not interact specifically with the pathophysiology associated with MH may trigger MH through a non-specific stress induced by the new drug or in combination with other drugs. The infusion of Atracurium for one hour in MH susceptible pigs does not initiate or provoke any of the pathophysiological responses associated with the MH syndrome except an increase in heart rate. The slight increase in heart rate we observed was statistically significant at the $p < .08$ level. We concluded that Atracurium should not trigger MH. Our data and conclusions are in agreement with a short note reporting no adverse effects of Atracurium in two MH susceptible pigs (4).

Title: MECHANISMS OF ARRHYTHMIAS DURING BUPIVACAINE INTOXICATION IN RABBITS - IN VITRO AND IN VIVO STUDY

Authors: JA Wojtczak, M.D., RM Griffin, M.D., V Pratilas, M.D., JA Kaplan, M.D.

Affiliation: Department of Anesthesiology, Mount Sinai School of Medicine, One Gustave L. Levy Place,
New York, New York 10029

Introduction. Intravenous injection of bupivacaine (Marcaine) during regional anesthesia is often associated with convulsions, serious cardiac arrhythmias and death.[1] We have studied the mechanisms of cardiac arrhythmias during bupivacaine (BUP) intoxication, comparing data from experiments on isolated cardiac tissue with in vivo data.

Methods. Female rabbits (2-4 kg) were immobilized and EKG needle electrodes inserted subcutaneously under local anesthesia. The marginal ear vein was cannulated under local anesthesia and BUP was injected intravenously in small boluses of 1-5 mg/kg every 15 or 30 min. Animals with life threatening arrhythmias and convulsions were treated and resuscitated (catecholamines, lidocaine, thiamylal, bicarbonate, hypertonic glucose and insulin, artifical ventilation.) In another series of rabbits, hearts were excised from animals previously anesthetized with thiamylal. Right atria, Purkinje fibers (PF) and papillary muscles were excised. The excised tissue was perfused in a small volume perfusion chamber with Tyrode's solution (4 mM K, 2.7 mM Ca, temp. 37 C), gassed with 95% O_2/5% CO_2. Transmembrane potentials were recorded with intracellular glass microelectrodes. Automatic activity of the sinus node was recorded either directly or by monitoring the rate of the spontaneously beating right atria. PF were stimulated at different rates from 30 to 150/min. Conduction velocity in PF was measured with two microelectrodes impaled at a constant distance away from the stimulation electrode. Preparations were exposed sequentially to BUP (1-10 mg/l) for 30 sec up to 60 min. Data were analyzed statistically by Student's "t" test ($P < 0.05$ significant).

Results. Two types of arrhythmic responses to BUP in unsedated rabbits were observed. Typically, they responded with tachyarrhythmias (Fig. 1a) in the form of sinus tachycardia which gradually (as the concentration of BUP increased) converted to nodal or ventricular tachycardia. The second type of arrhythmic response (Fig. 1b) was characterized by transient sinus tachycardia followed by sinus bradycardia with prolongation of P-R interval and periods of sinus arrest. Both types of arrhythmias could be considered as premonitory signs of the next irreversible phase with rapidly developing bradycardia, premature beats (Fig. 1c) with advanced A-V block, and large QRS complexes. Pharmacological treatment at this stage was rarely effective. In vitro studies showed that BUP markedly slows conduction velocity at different levels of the conduction system, and in atrial and ventricular muscle. Conduction velocity in PF was significantly reduced, particularly at the higher frequency of stimulation (Fig. 2). Sinus node automaticity (phase 4) was consistently depressed with the frequent occurrence of sinoatrial conduction block in the isolated right atria. In PF, phase 4 automaticity was completely suppressed by BUP even in very low concentrations (1 mg/l).

Discussion. Comparison of the in vitro and in vivo studies shows that cardiac arrhythmias occurring during BUP intoxication are due to generalized slowing of the conduction velocity and suppression of pacemaker activity in the conduction system. Slowed conduction enhances formation of the rapidly firing reentrant circuits which are probably responsible for the nodal and ventricular tachycardias observed in the first type of response. Further slowing of the conduction velocity inhibits reentrant circuits with the emergence of pronounced bradycardia and long QRS complexes. Nodal and ventricular tachycardia cannot be due to increased ventricular automaticity which is easily suppressed by BUP. Sinus automaticity is markedly suppressed by BUP, however, sinus bradycardia observed in some rabbits may also be due to the marked sinoatrial conduction block. The dominant initial tachycardic type of response to BUP with long bursts of sinus tachycardia can only be explained by adrenergic reversal of the direct BUP effects on the sinus node. This reflex adrenergic response is probably due to the peripheral vasodilation induced by the increasing concentrations of BUP.

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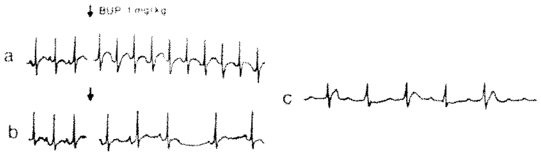

Figure 1. Effects of BUP on the EKG of unsedated rabbits, a-type I response (nodal tachycardia), b-type II response (bradycardia with sinus arrest), c-irreversible, terminal phase.

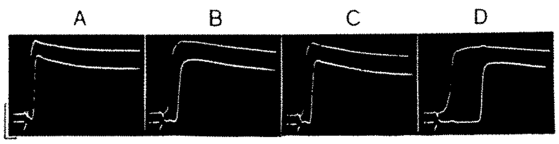

Figure 2. Effects of BUP (5 mg/l) on the interelectrode conduction time (ICT) at different rates of stimulation. Upstrokes of the action potentials shown at fast sweep speed of the oscilloscope. A-control at 60/min (ICT-3.4 sec), B-30 min of superfusion with BUP at 60/min (ICT-7.1 sec), C-control at 120/min (ICT-4.9 sec). D-30 min of superfusion at 120/min (ICT-22.5 sec). Vertical calibration 50 mV, horizontal 5 msec.

Title: EFFECTS OF GENERAL AND LOCAL ANESTHETICS ON INTERCELLULAR ELECTRICAL COUPLING IN HEART MUSCLE

Authors: J.A. Wojtczak, M.D. and J.A. Kaplan, M.D.

Affiliation: Department of Anesthesiology, Mount Sinai School of Medicine, One Gustave L. Levy Place,
New York, New York 10029

Introduction. Electrical coupling and transmission of excitation between neighboring cells in heart muscle is ascertained by the existence of low-resistance intercellular channels called gap junctions. A decrease in the degree of cell-to-cell coupling may induce disturbances of synchronous discharge in the pacemaker region, produce slow conduction or even conduction block. This study evaluated the influence of various anesthetic drugs on inter-cellular coupling in normal and calcium overloaded preparations.

Methods. Papillary muscles were excised from the right ventricles of feline and canine hearts. They were superfused with Tyrode solution gassed with 95% O_2 -5% CO_2. Changes in intercellular coupling were evaluated by measuring internal longitudinal resistance (r_i) using either the oil-gap method[1] or modified sucrose-gap method[2]. In the oil-gap method extracellular and intracellular potentials were recorded with glass microelectrodes. In the sucrose gap method relative changes in trans-gap potential (TGP)(Fig.1) were measured and its amplitude in control conditions was taken as 100% of coupling. In the oil-gap method twitch and resting tension developed by the muscles were also measured. Halothane and diethyl ether were vaporized whereas alcohols and local anesthetics were directly dissolved in Tyrode solution. Data were analyzed statiscally by Student "t" tests ($P < 0.05$ significant).

Results. Halothane (2%-3%) and medium-chain alcohols (1-5 mM hexanol, heptanol, octanol and phenol) produced fast and reversible uncoupling. Ether even in high concentrations (15-50mM) exerted no effect. Lidocaine (10^{-4}M) and droperidol (10^{-4}M) which exerts local anesthetic effects similar to lidocaine, did not affect coupling in the normal preparations during 30-60 min exposure. Trifluoperazine (10^{-4}M) which as a chlorpromazine derivative also exerts pronounced local anesthetic effects, did not affect coupling in the normal preparations. These drugs were also tested in calcium overloaded preparations. Calcium overloading was induced by superfusion for 30 min with 400% hypertonic sucrose solutions. Such treatment transiently disrupts cell membranes inducing influx of calcium. Contracture (increase in resting tension) and electrical uncoupling induced by this superfusion could be partly prevented by pretreatment for 45 min with lidocaine or droperidol, and prevented by Trifluoperazine (TFP). The difference was statistically significant. However, TFP was unable to prevent electrical uncoupling induced by halothane and alcohols (Fig.1)

Discussion. It was shown previously that intercellular uncoupling is produced by calcium overloading during hypoxia/ischemia or during digitalis intoxication. In this study we have shown that electrical uncoupling can also be produced by halothane. This finding may explain inhibitory effects of halothane on intraventricular conduction and its arrhythmogenic influences. Local anesthetics which are commonly used as antiarrhythmic drugs, while exerting no effect on coupling in normal preparations, can prevent uncoupling produced by calcium overloading. Strong preventive action of TFP may be due to the fact that this neuroleptic is a relatively potent inhibitor of calmodulin, the protein mediating biological effects of calcium inside the cells. Indirectly it implies that calmodulin may be involved in calcium-induced uncoupling and that inhibition of calmodulin activity may prevent this type of uncoupling, suggesting that new, more specific calmodulin inhibitors may be very effective as antiarrhythmic drugs. Uncoupling produced by halothane and alcohols could not be prevented by TFP. As these substances produce strong negative inotropic effects and relaxation rather than contracture, a possibility of calcium overloading produced by these substances is certainly excluded. This result suggests that electrical uncoupling produced by halothane and alcohols depends on a different mechanism (direct action on channel forming proteins?) which is not dependent on interaction of calcium with gap junctions.

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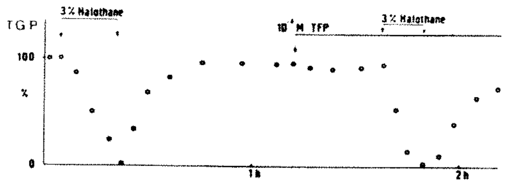

Figure 1. Effects of halothane and trifluoperazine (TFP) on intercellular electrical coupling (TGP).

Title: COMPARATIVE STUDY BETWEEN NITROPRUSSID AND KETANSERIN IN THE TREATMENT OF HYPERTENSION FOLLOWING CORONARY ARTERY BYPASS GRAFTING.

Authors: P.J.A. van der Starre, M.D. and J. Harinck-de Weerd, M.D.

Affiliation: Department of Anesthesia , Medical Center De Klokkenberg, Breda, The Netherlands.

Introduction. The incidence of postoperative hypertension following coronary artery bypass grafting (CABG), is reported between 30 and 60%, and mainly due to raised levels of catecholamins, renin/angiotensin and possibly 5-hydroxytryptamin, causing an increase in systemic vascular resistance (1). Nitroprussid and ketanserin have been reported to be effective in the treatment of this kind of hypertension (3,4). In a clinical study both agents were compared with respect to the haemodynamic responses and changes in shuntfraction (Qs/Qt).

Methods. Two groups of 10 patients, comparable in sex, age, weight and duration of extracorporeal circulation, who had undergone CABG, were treated with either nitroprussid (N) (1,5 mg/kg/min) or ketanserin (K) (10 mg + 0.1 mg/kg/hr), when the systolic blood pressure (SBP) had increased postoperatively to 150 mmHg. The following haemodynamic values were measured before and following 30 minutes of treatment: SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), systolic pulmonary artery pressure (SPAP), diastolic pulmonary artery pressure (DPAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), heartrate (HR), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR). At the same time Qs/Qt was determined after the patients were ventilated with $FIO_2=1.0$ during 5 minutes. From all patients informed consent was obtained; the study was approved by the ethical committee of the hospital.Statistical analysis was performed using Wilcoxon-MPSR/analysis (intragroup) and Mann-Whitney U-test (intergroup).

Results. In the N-group SBP, MAP, DPAP, MPAP, SVR, PVR, decreased, and CI increased significantly, proportional to the K-group, but HR and Qs/Qt increased significantly in the N-group ($p < 0.05$), and not in the K-group (fig. 1).

Discussion. The treatment of postoperative hypertension following CABG, a well-known phenomenon (2), consists generally of the use of vasodilating agents like nitroprussid, nitroglycerin, trimetaphan or hydralazin (1,4). In this study in which nitroprussid was compared with ketanserin, both agents appeared to be effectively antihypertensive by decreasing the raised systemic vascular resistance with comparable haemodynamic responses, but ketanserin, a 5-hydroxytryptamin antagonist with alpha-blocking properties (4), caused no reflextachycardia or increase of Qs/Qt, as was the case with nitroprussid. Especially in patients with a jeopardized myocardium or pulmonary dysfunction, this feature might be advantageous in preventing an increase in myocardial oxygen consumption and/or hypoxia.

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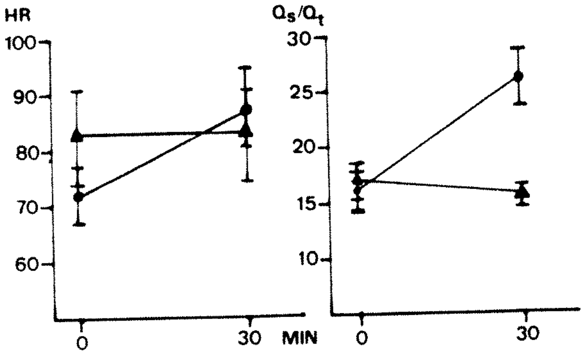

Fig. 1: ▲ = ketanserin-group
● = nitroprussid-group

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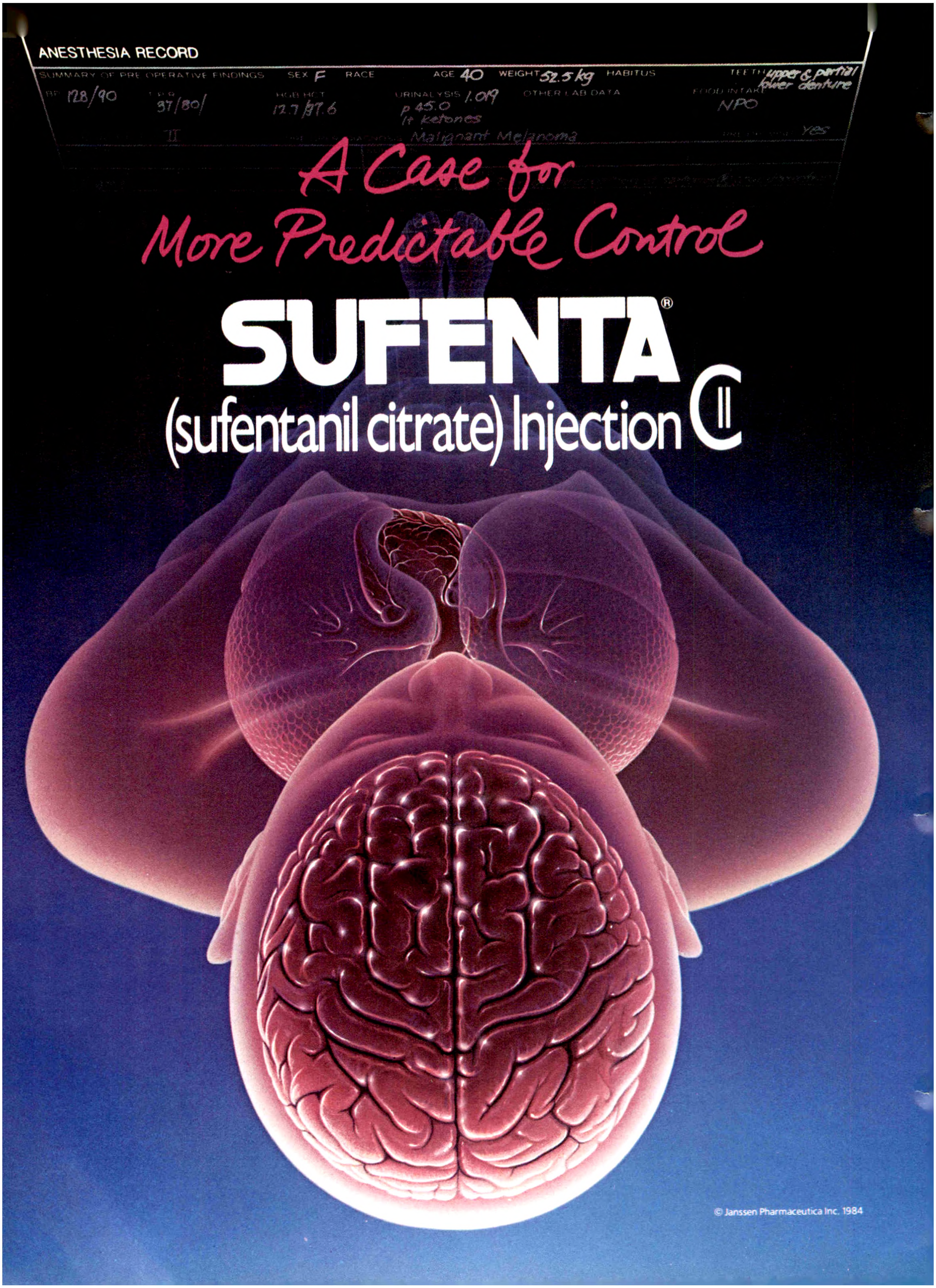

ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS SEX F RACE AGE 40 WEIGHT 52.5 kg HABITUS TEETH upper & partial lower denture

BP 128/90 T.P.R. 37/80/ HGB HCT 12.7/37.6 URINALYSIS 1.019 p 45.0 1+ ketones OTHER LAB DATA FOOD INTAKE NPO

II DIAGNOSIS Malignant Melanoma YES

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...More Predictable Control from Induction through Recovery

COMPARED WITH ISOFLURANE*[1,2]

- Superior hemodynamic stability
- Shorter recovery times
- Better maintenance of postoperative analgesia
- Lower total cost per procedure

*In a comparative study[1,2] of patients undergoing major orthopedic surgery who received either SUFENTA-N_2O (n=10) or isoflurane-N_2O (n=10).

1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.
2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

COMPARED WITH FENTANYL[3,4]

- Smoother, more rapid induction
- Smoother, more stable intraoperative course
- Faster, more comfortable recovery
- More effective blocking of surgical stress response
- Superior hemodynamic stability
- Smaller volume of injection
- Lower total cost per procedure

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PHARMACEUTICA

SUFENTA®
(sufentanil citrate) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be ¼-⅐ those of fentanyl on a mg/kg basis.) At doses of up to 8 μg/kg, SUFENTA provides profound analgesia; at doses ≥8 μg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 μg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 μg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 μg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 μg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 μg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 μg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 μg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 μg/kg in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 μg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 μg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 μg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 μg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
1-2 μg/kg: administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 μg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
2-8 μg/kg: administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
8-30 μg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 μg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 μg/kg, catecholamine release is attenuated. Dosages of 25-30 μg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 μg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 μg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 μg/ml, 5 ml ampoules in packages of 10

Protect from light. Store at room temperature.

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854
7618500
U.S. Patent No. 3,998,834
May 1984

PACKAGED FOR SPECIAL DELIVERY

ANECTINE
NDC-0081-0071
10 cc Multiple-dose Vial
ANECTINE Brand
SUCCINYLCHOLINE CHLORIDE INJECTION
20 mg in each cc
CAUTION: Federal law prohibits dispensing without prescription
Store under refrigeration
BURROUGHS WELLCOME CO.
Research Triangle Park, N.C. 27709
500 mg
ANECTINE
SUCCINYLCHOLINE CHLORIDE
STERILE POWDER
FLO-PACK
for preparation of intravenous drip solution
CAUTION: Federal law prohibits dispensing without prescription
BURROUGHS WELLCOME CO.
RESEARCH TRIANGLE PARK, N.C.

The Anectine Flo-Pack® *needs no refrigeration and mixes instantly with diluent. No separate needle or syringe is necessary. And, both the 500 and 1000 mg sizes work equally well with either bottles or bags.*

The Anectine 20 mg Bottle
has a unique square shape for added safety and a convenient flip-off top for speed of use. The distinctive yellow and red label can be read from the reverse side for instant identification.

Only ANECTINE®
(succinylcholine chloride)
Delivers the Kind of Ease and Convenience You Need

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

for prolonged procedures:

Mastectomy

Coronary Bypass

Hysterectomy

prolonged action can be a plus.

Premedication with Ativan® (lorazepam) Injection may well be the most logical choice for longer surgical procedures where extended sedation and / or lack of recall are especially desirable.

A single injection of Ativan Injection provides dependable sedation for 6-8 hours. When surgery runs longer than anticipated, or unexpected delays occur, repeated injections may not be required.

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Hip Replacement

Cholecystectomy

Knee Surgery

Head and Neck

Administered as recommended, Ativan Injection allays preoperative apprehension, relieves anxiety, leaves patients calm but cooperative and diminishes recall of events surrounding surgery. There is little, if any, IV irritation at proper dilution, and only minimal effects on blood pressure, pulse or respiratory rate.

The dosage of Ativan® (lorazepam) Injection should be individualized for each patient. For those in whom reduced recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom lack of recall is not desired, and for the elderly or debilitated, the dose should be reduced.

ATIVAN® (LORAZEPAM) Ⓒ
INJECTION IM or IV

See important information on following page.

Wyeth Laboratories
Philadelphia, PA 19101

ATIVAN® (LORAZEPAM) ⒸIV
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam Injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) Injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

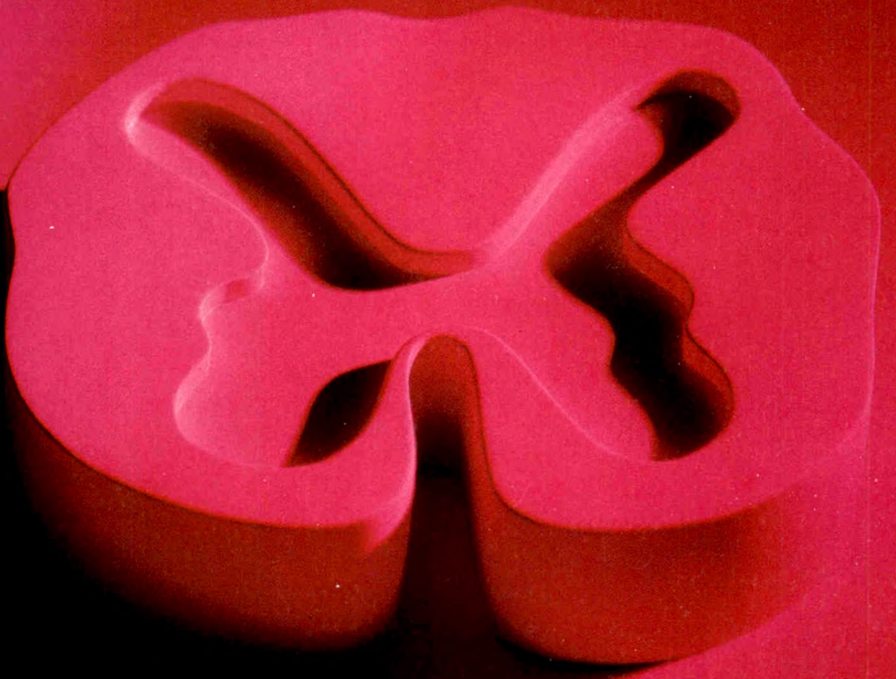
Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogeneous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101
TM

CI 3117-1 7/31/80

A first in selective spinal analgesia:

The discovery of opiate receptors in the dorsal horn of the spinal cord has created exciting new options in pain management.

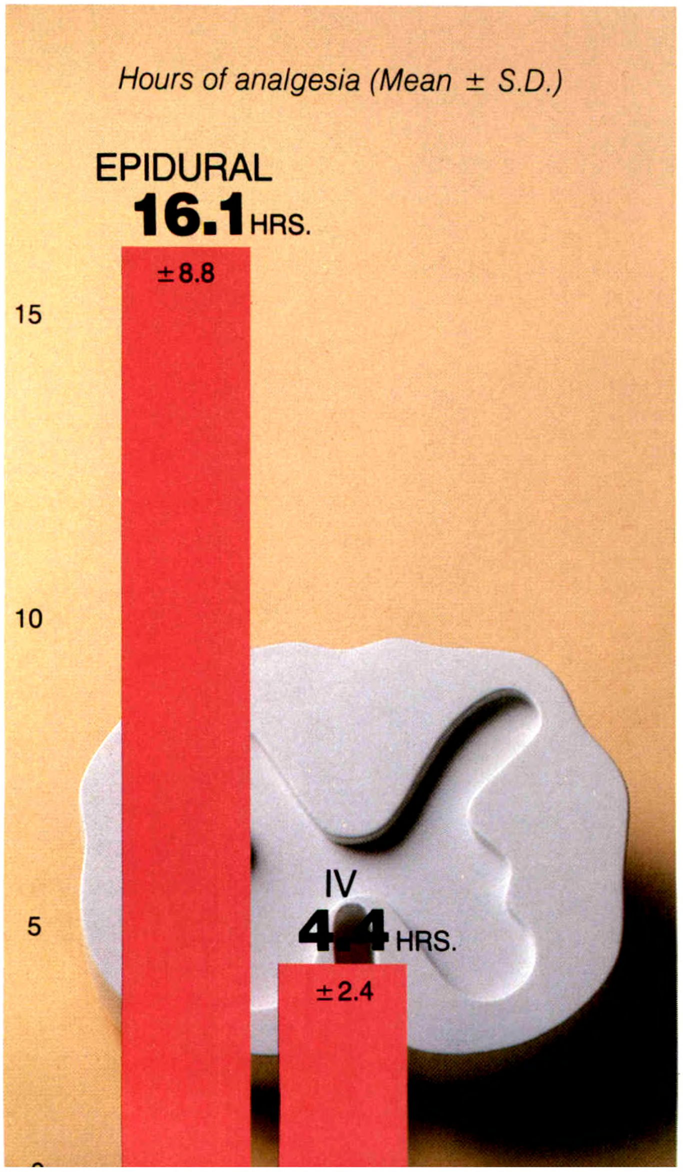


A·H·ROBINS

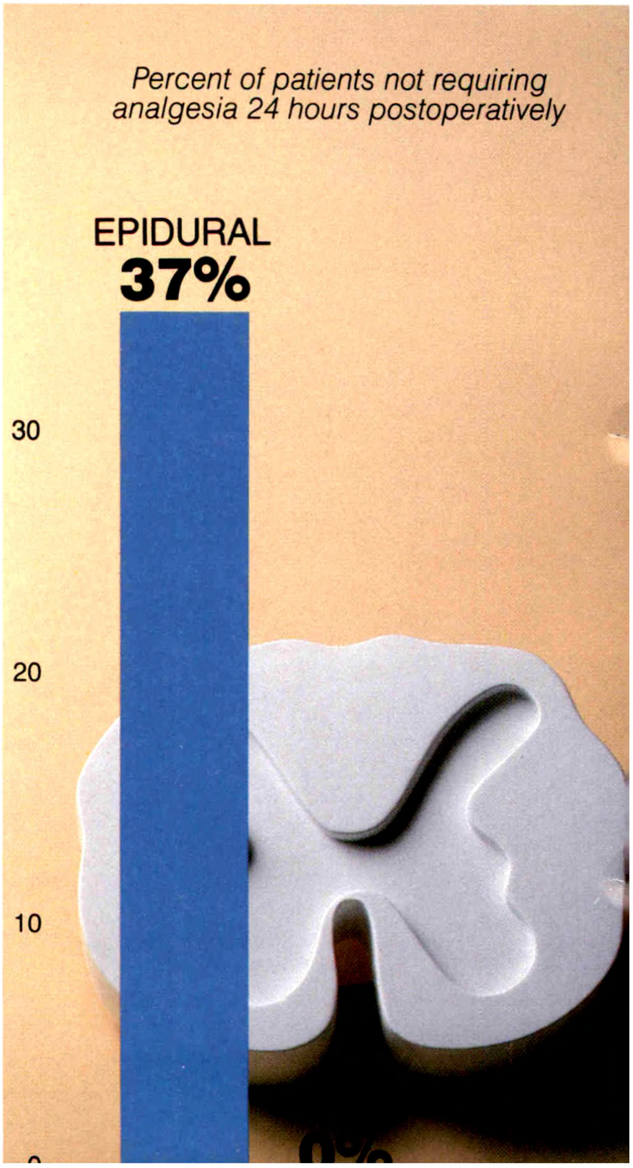
Prolonged postoperative analgesi with a single epidural injection . . .

DURAMORPH® PF PROVIDES SUPERIOR ANALGESIA WHEN COMPARED WI

DURATION OF PAIN RELIEF IS NEARLY QUADRUPLED



POSTOPERATIVE ANALGESIA OFTEN LASTS UP TO 24 HOURS



PRESERVATIVE-FREE

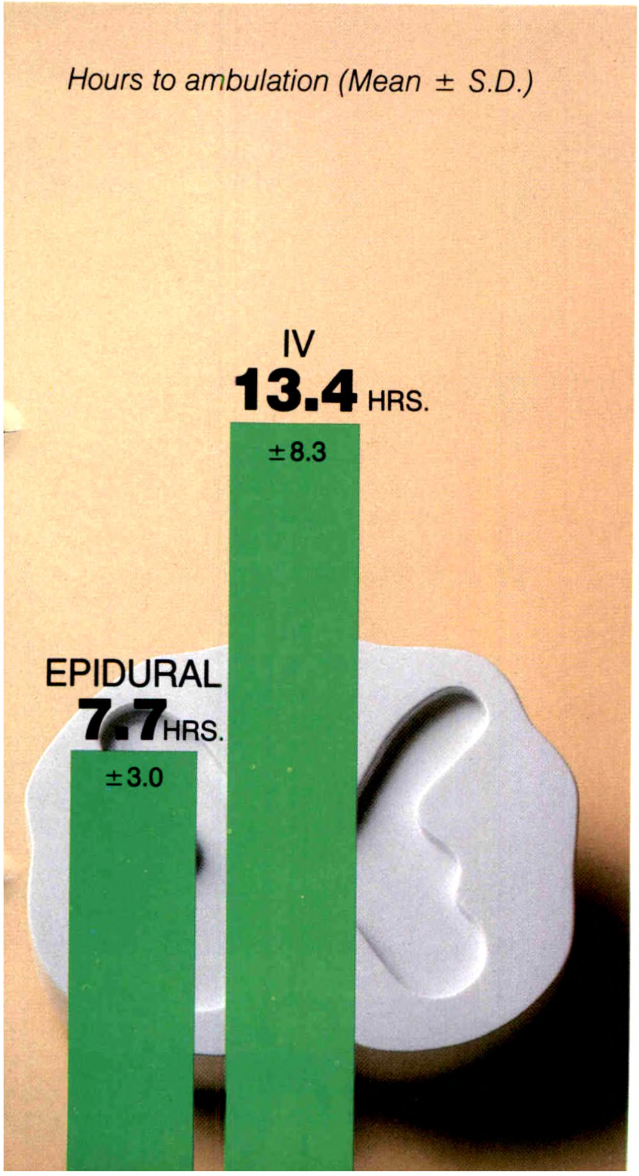
Duramorph® PF

morphine sulfate injection, USP) C II

ONVENTIONAL NARCOTIC ADMINISTRATION:

OSTOPERATIVE ATIENTS MAY E AMBULATORY N HALF THE TIME

*Charts depict the results of a double-blind study comparing the analgesic efficacy of 5 mg epidural morphine (N = 19) with that of 5 mg intravenous (IV) morphine (N = 19) following cesarean section.**



- **Virtually no sedation or loss of motor function**
  DURAMORPH® PF administered epidurally relieves pain with little effect on sensory, motor or sympathetic function. Patients are alert, cooperative and able to move about without discomfort.
- **No potentially neurotoxic additives**
  Unlike other morphine preparations, DURAMORPH® PF contains no bisulfites, phenols, chelating agents, paraben preservatives, or benzyl alcohol that may cause neurotoxicity when administered epidurally.
- **Low incidence of respiratory depression**
  Delayed respiratory depression has been reported. Patients should be monitored closely for 24 hours postoperatively after each dose. If respiratory depression should occur, it can be reversed readily with naloxone, without affecting the quality of analgesia.

*Cohen SE, Woods WA: Anesthesiology 58:500, 1983

esi
Elkins-Sinn, Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08034
800-257-8349

A subsidiary of A·H·ROBINS

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PRESERVATIVE-FREE
Duramorph® PF
(morphine sulfate injection, USP) CII

DESCRIPTION

Preservative-free DURAMORPH® PF (Morphine Sulfate Injection, USP) is a sterile, pyrogen-free, isobaric solution free of antioxidants, preservatives or other potentially neurotoxic additives, and is intended for intravenous, epidural or intrathecal administration as a narcotic analgesic. Each milliliter contains morphine sulfate 0.5 mg or 1 mg (Warning: May Be Habit Forming) and sodium chloride 9 mg in Water for Injection. pH range is 2.5-6.0. Ampuls are sealed under nitrogen. Each Dosette® ampul is intended for SINGLE USE ONLY. Discard any unused portion. DO NOT AUTOCLAVE.

INDICATIONS AND USAGE

Preservative-free DURAMORPH® PF is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

CONTRAINDICATIONS

DURAMORPH® PF is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

WARNINGS

DURAMORPH® PF administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.

FACILITIES WHERE DURAMORPH® PF IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.

SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.

Morphine sulfate may be habit forming. (See Drug Abuse and Dependence section.)

PRECAUTIONS

GENERAL

Preservative-free DURAMORPH® PF (Morphine Sulfate Injection, USP) should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial/intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis).

Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

It is recommended that administration of DURAMORPH® PF by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to risks inherent in urethral catheterization, e.g., sepsis, when epidural or intrathecal administration is considered, especially in the perioperative period.

Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

DRUG INTERACTIONS

Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY

Teratogenic effects—Pregnancy Category C. Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.

Nonteratogenic effects. Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

LABOR AND DELIVERY

Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

Epidurally and intrathecally administered morphine readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that *epidural* administration has little or no effect on the relief of labor pain.

However, studies have suggested that in most cases 0.2 to 1 mg of morphine *intrathecally* provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr, for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

NURSING MOTHERS

Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most serious side effect is respiratory depression. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (See Warnings and Overdosage sections). Even without clinical evidence of ventilatory inadequacy, a diminished CO_2 ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.

Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10-20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see Precautions). Pruritus, nausea/vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).

Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see Drug Abuse and Dependence section).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as uticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Morphine sulfate is a Schedule II substance under the Drug Enforcement Administration classification.

Abuse: Morphine has recognized abuse potential.

Dependence: Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Nonteratogenic effects under Pregnancy.)

OVERDOSAGE

Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, simultaneously with respiratory resuscitation. *As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary.* Patients should be closely observed for evidence of renarcotization. *Note: Respiratory depression may be delayed in onset up to 24 hours* following epidural or intrathecal administration. In painful conditions, reversal of narcotic effect may result in acute onset of pain and release of catecholamines. Careful administration of naloxone may permit reversal of side effects without affecting analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

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Editor: **Edmond I. Eger II, M.D.,** Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco

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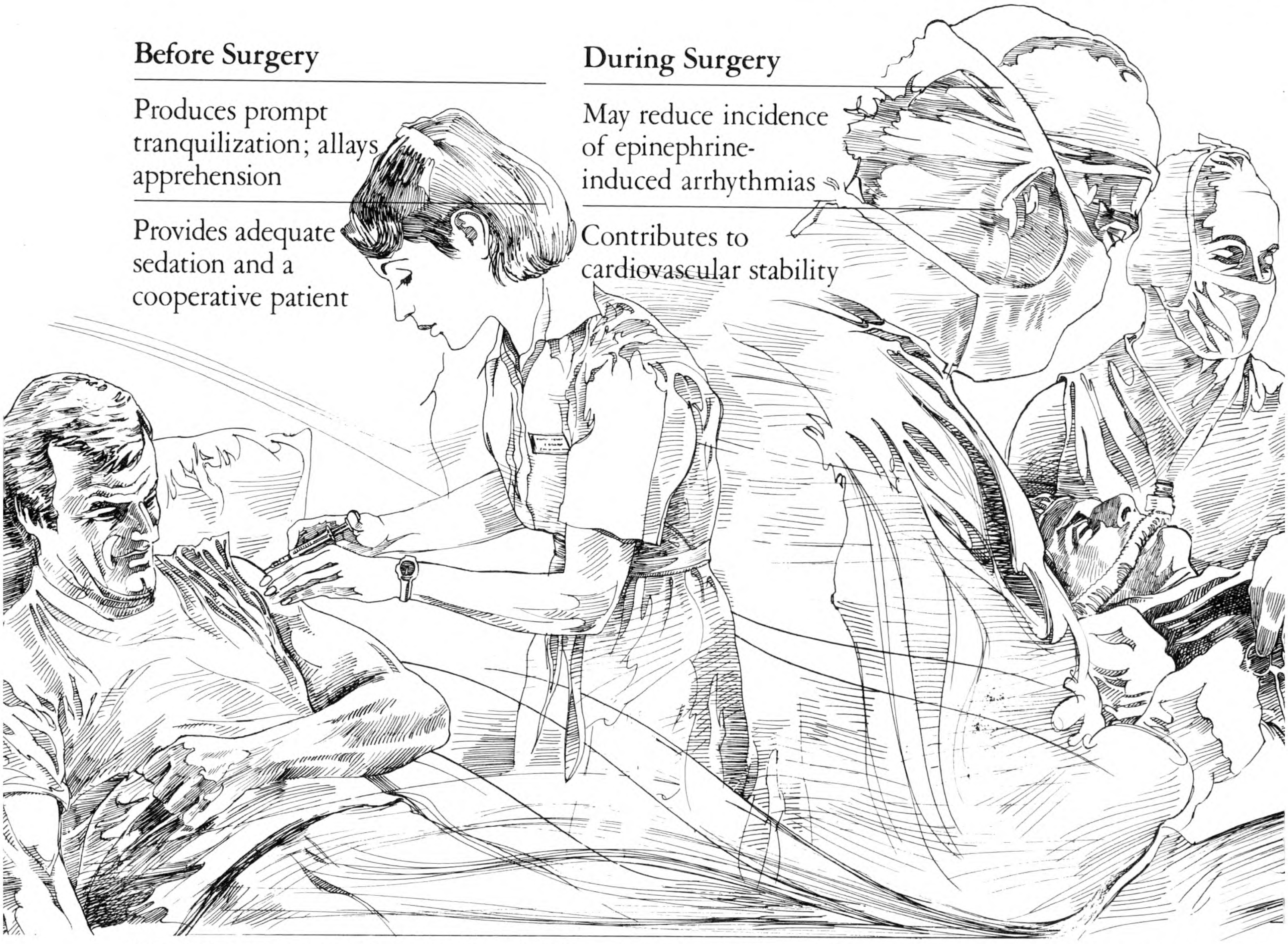
The premedication that well into the



Before Surgery

Produces prompt tranquilization; allays apprehension

Provides adequate sedation and a cooperative patient

During Surgery

May reduce incidence of epinephrine-induced arrhythmias

Contributes to cardiovascular stability

Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:
2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol . . . . 2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol . . . . 2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

goes on helping... postoperative period

After Surgery

Exerts potent antiemetic effect

Reduces need for postoperative narcotics

Inapsine®

(droperidol) Injection

The premedication that does more than premedicate

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur.

Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR® injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: 2 ml. and 5 ml. ampoules—packages of 10;
10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980
*See full prescribing information for complete description.
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JPI-342

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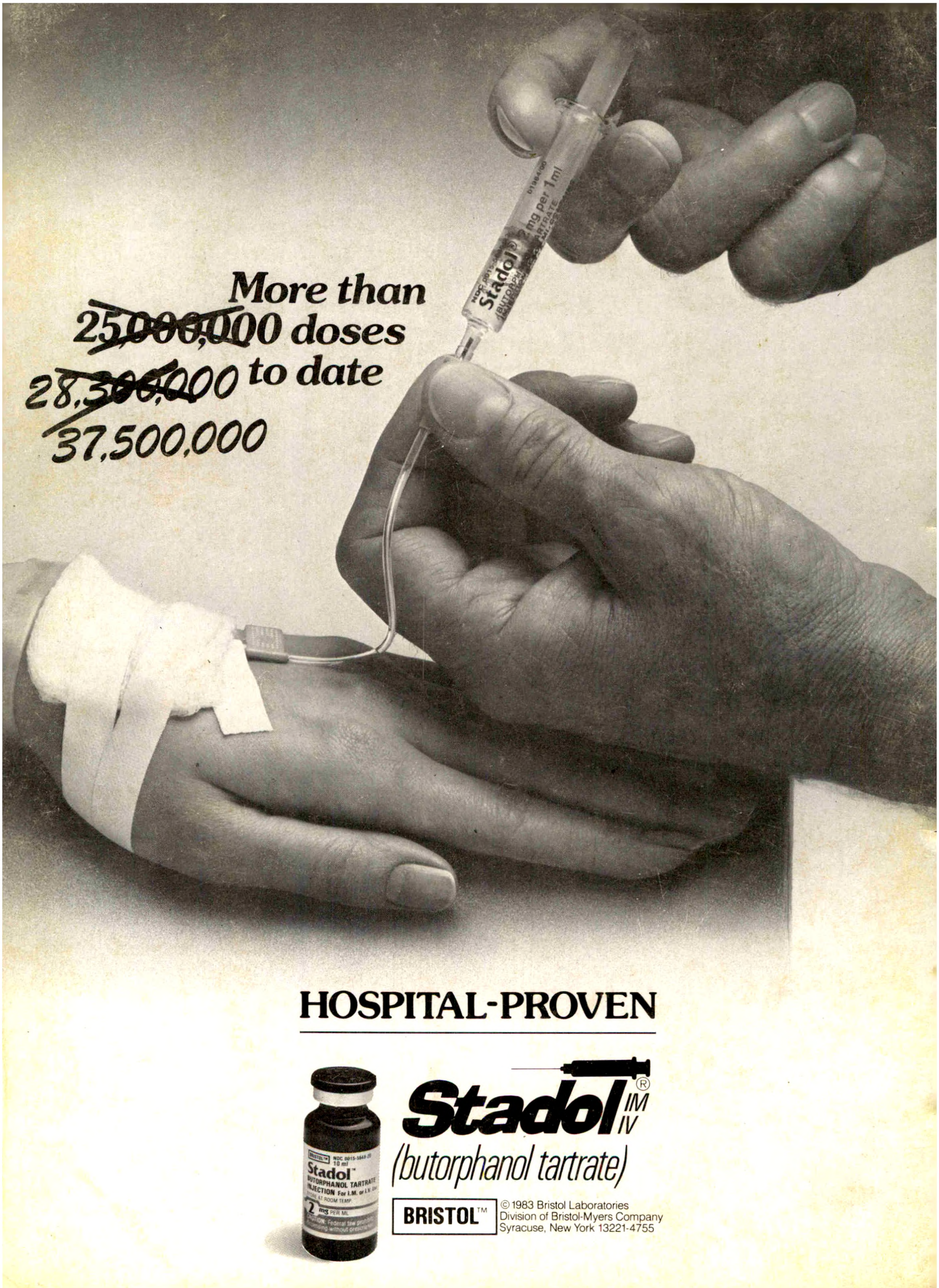

More than ~~25,000,000~~ doses
~~28,300,000~~ to date
37,500,000

HOSPITAL-PROVEN

Stadol® IM IV
(butorphanol tartrate)

BRISTOL™

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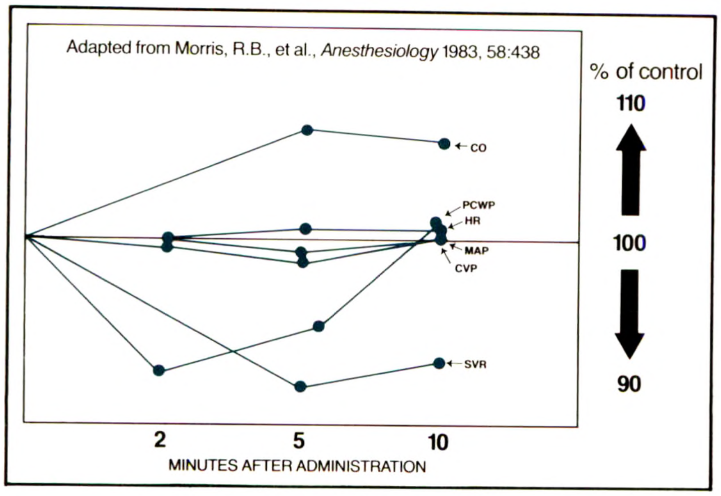
Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
WE STRIVE ALWAYS FOR WORLD CONQUEST OF PAIN
1922

In neuromuscular blockade…
Closest to the ideal:


Adapted from Morris, R.B., et al., *Anesthesiology* 1983, 58:438

Free of clinically significant cardiovascular effects

NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.[1-3] This makes NORCURON unique among all neuromuscular blocking agents in clinical use.[4]

The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate[5]

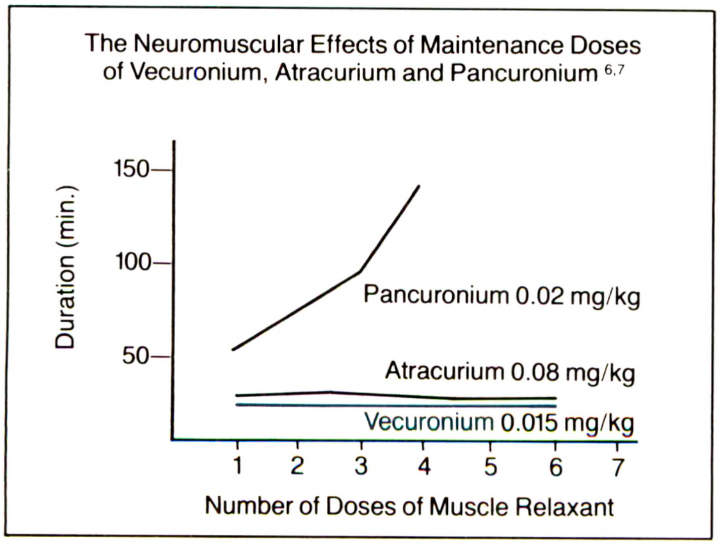
Drug	Dose (mg/kg)	xED_{95}	Percent of Control Histamine	 Mean Arterial Pressure	 Heart Rate
tubocurarine	0.5	1	318	78	116
metocurine	0.5	2	212	79	119
atracurium	0.6	3	192	80	108
vecuronium	0.1	1.7	117	100	99
vecuronium	0.2	3.5	87	99	102

Histamine release unlikely to occur

Histamine release has not been observed with NORCURON…as shown by preliminary clinical experience. In doses up to 3.5 times the ED_{95}, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.[5]

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.[5]

The Neuromuscular Effects of Maintenance Doses of Vecuronium, Atracurium and Pancuronium[6,7]



No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.[6,7]

NORCURON®

(vecuronium bromide for injection)

Safety Index and Comparative Safety Ratios[8]

$$\text{Safety Index} = \frac{\text{ED}_{50}\text{ autonomic inhibition}}{\text{ED}_{95}\text{ neuromuscular blockade}}$$

Comparative Safety Ratios

For Vagolytic Effects		For CV/Histamine Related Effects	
gallamine	1:1	d-tubocurarine	1:1
pancuronium	3:1	metocurine	2:1
atracurium	25-30:1	atracurium	3:1
vecuronium	60:1	vecuronium	*

*cannot be calculated since it does not cause any CV or histamine related effects

Outstanding safety profile

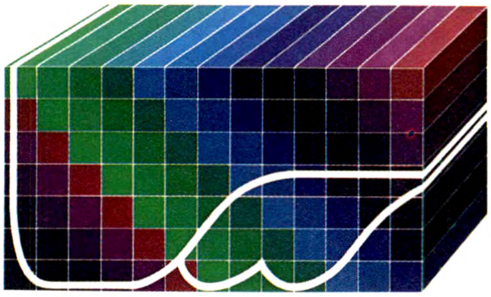
The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.[8]

The Safety Index is described as the ED_{50} for autonomic inhibition over the ED_{95} for neuromuscular blockade.[8]

A Comparison of Surgical Muscle Relaxants vs. The Ideal[4]
(" + " signifies proximity to the ideal)

Characteristic	Vecuronium	Atracurium	Pancuronium	Succinylcholine	D-tubocurarine
Onset of Action	–	–	–	+	–
Histamine Release	+	–	+	+	–
Cardiovascular Side Effects	+	+ / –	–	–	–
Duration of Action	+	+	–	+	–
Cumulative Effects	+	+	–	–	–
Rate of Recovery	+	+	–	+	–
Reversibility	+	+	+	–	+
Potency	+	+	+	–	–
Non-depolarizing	+	+	+	–	+
Metabolite Activity	+	+*	+	+	+

*Currently under evaluation.



NORCURON®
(vecuronium bromide for injection)

Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.[4]

Organon

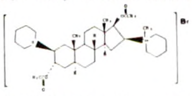
1. Durant NN: Norcuron®—A new non-depolarizing neuromuscular blocking agent. *Semin Anesth* 1:47-56, 1982. **2.** Morris RB, Cahalan MK, Miller RD, et al: Cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC45, pancuronium, alcuronium, and tubocurarine in anaesthetized man. *Br J Anesth* 52:783-787, 1980. **4.** Miller RD (ed): *Innovations in Surgical Muscle Relaxants*. Far Hills, NJ, Gardiner-Caldwell Synermed, 1984. **5.** Basta SA, Savarese JJ: Comparative histamine-releasing properties of vecuronium, atracurium, tubocurarine and metocurine, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC45, vecuronium bromide)*. Amsterdam, Excerpta Medica, 1983, p. 183. **6.** Foldes FF, et al: Muscular relaxation with atracurium, vecuronium and Duodor under balanced anaesthesia. *Br J Anaesth* 55 (suppl. 1): 97S, 1983. **7.** Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (Norucon®): a new non-depolarizing muscle relaxant. *Anesthesiology* 55:6, 1981. **8.** Clinical Courier, Vol. 2, No. 4, July 1984.

NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis (acetyloxy)-2-(1- piperidinyl) androstan-16-yl]-1-methyl-, bromide. The structural formula is:



Norcuron® is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron® (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron® (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide for injection).

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron® (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron® (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® (vecuronium bromide for injection) is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringers

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10

STORAGE: PROTECT FROM LIGHT Store at 15°-30°C (59°-86°F)

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

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Premedication with Ativan® (lorazepam) Injection may well be the most logical choice for longer surgical procedures where extended sedation and/or lack of recall are especially desirable.

A single injection of Ativan Injection provides dependable sedation for 6-8 hours. When surgery runs longer than anticipated, or unexpected delays occur, repeated injections may not be required.

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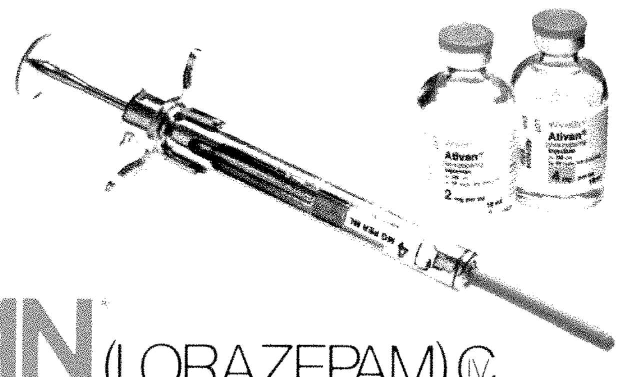
Administered as recommended, Ativan Injection allays preoperative apprehension, relieves anxiety, leaves patients calm but cooperative and diminishes recall of events surrounding surgery. There is little, if any, IV irritation at proper dilution, and only minimal effects on blood pressure, pulse or respiratory rate.

The dosage of Ativan® (lorazepam) Injection should be individualized for each patient. For those in whom reduced recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom lack of recall is not desired, and for the elderly or debilitated, the dose should be reduced.



ATIVAN (LORAZEPAM) Ⓒ IV

INJECTION IM or IV

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ATIVAN® (LORAZEPAM) Ⓒ IV
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101
TM

CI3117-1 7/31/80

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The Anectine Flo-Pack® *needs no refrigeration and mixes instantly with diluent. No separate needle or syringe is necessary. And, both the 500 and 1000 mg sizes work equally well with either bottles or bags.*

The Anectine 20 mg Bottle *has a unique square shape for added safety and a convenient flip-off top for speed of use. The distinctive yellow and red label can be read from the reverse side for instant identification.*

Only ANECTINE®
(succinylcholine chloride)
Delivers the Kind of Ease and Convenience You Need

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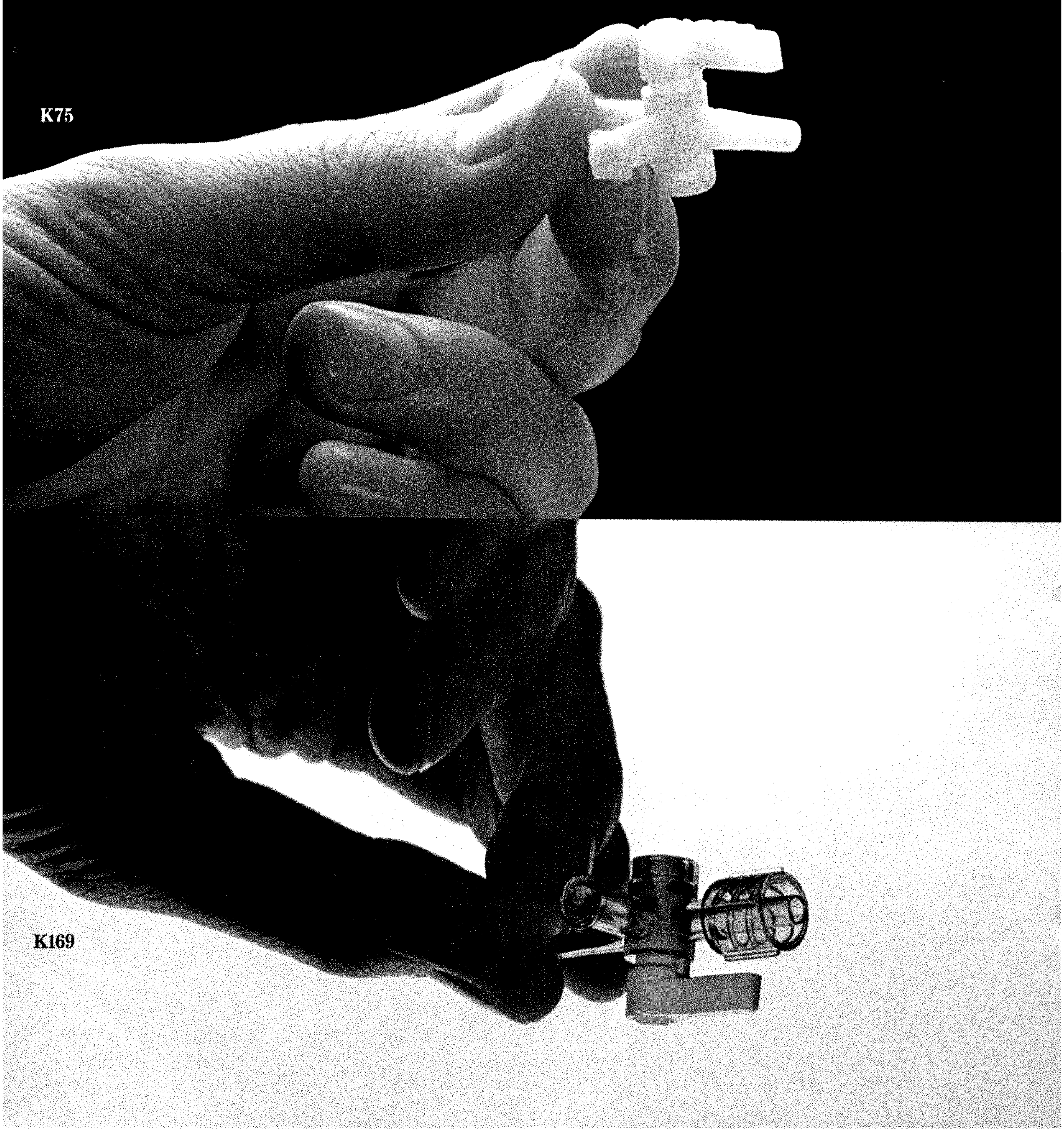
When it comes to stopcocks, hospitals have Pharmaseal's number.



“Get me a K75...”

We're American Pharmaseal, and we make great stopcocks. In fact, you may not even know that we make them, but you sure know about them.

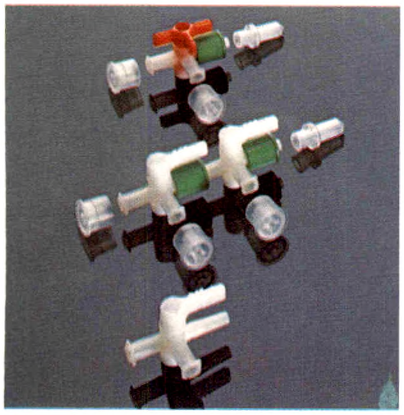
“Get me a K-75...” for example, is heard all day in hospitals all over the country.

Our K-75 and K-52 Novex® stopcocks are legendary. And they're only part of the most complete and widely used line of general purpose stopcocks available anywhere.

One-way...Three-way...Double and triple tandem three-way...

The K-52 Novex with injection port.

Stopcocks with special caps to protect ports. And with rotating Luer-lock adapters for proper alignment and secure connections.



Stopcocks with a choice of pre-attached extension tubes which add up to a virtually endless variety of possible applications.

All with smooth-turning handles that won't stick or leak in the usual applications.

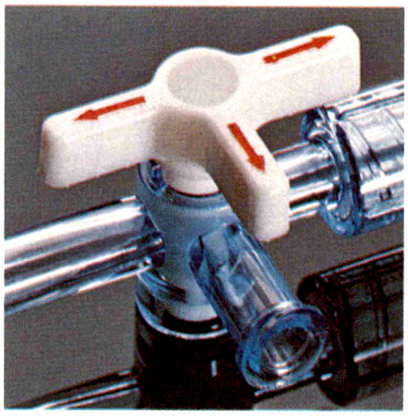
And now, a complete line of K-Series clear stopcocks for invasive monitoring.

Our latest innovation is the K-Series clear stopcocks designed for invasive monitoring.

The transparent light blue body makes air bubbles very easy to see with visual inspection. So there's no need to worry about hidden air bubbles.

The white handle has a convenient, comfortable shape that turns easily and smoothly. Plus, each handle is clearly labeled to identify the flow path.

These non-leaking stopcocks feature Luer-lock fittings. They're superb units, just what you need for invasive monitoring.



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That's how many we've made. That's a lot of experience.

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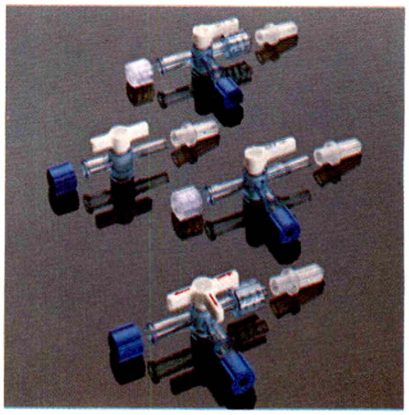
The result, highest quality American Pharmaseal stopcocks.

Our K-Series stopcocks. Now that you know who makes them, we may hear you saying, “Get me the *Pharmaseal*® K-75...”



For full details on our stopcocks and extension tubes including the numerous hookups available and the new invasive monitoring kits, contact your American Pharmaseal representative.

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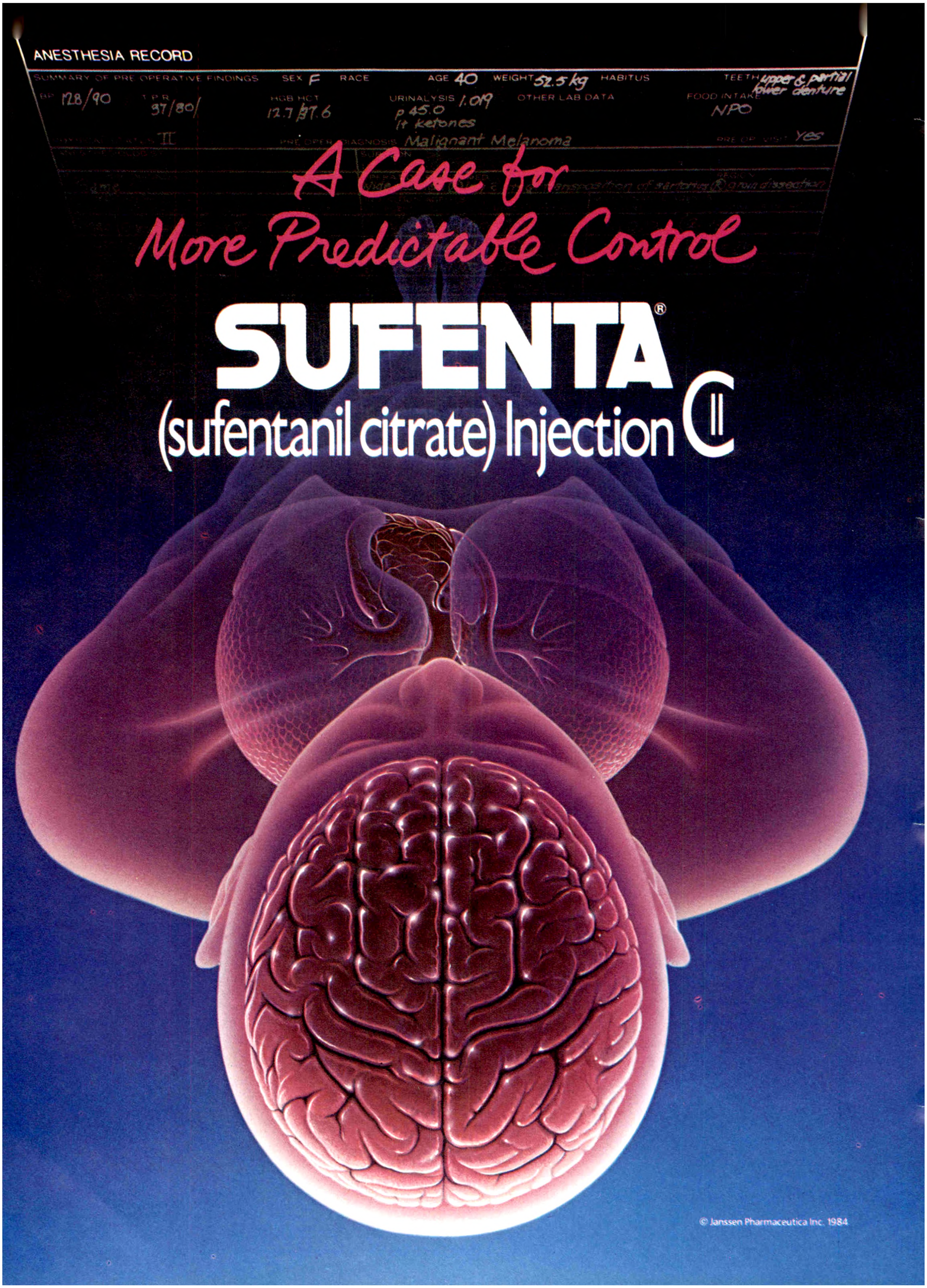

ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS SEX F RACE AGE 40 WEIGHT 52.5 kg HABITUS TEETH upper & partial lower denture

BP 128/90 T P R 37/80/ HGB HCT 12.7/37.6 URINALYSIS 1.019 p 45.0 1+ ketones OTHER LAB DATA FOOD INTAKE NPO

PHYSICAL STATUS II PRE OPER DIAGNOSIS Malignant Melanoma PRE OP VISIT Yes

transposition of sartorius (R) groin dissection

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...More Predictable Control from Induction through Recovery

COMPARED WITH ISOFLURANE*[1,2]

- Superior hemodynamic stability
- Shorter recovery times
- Better maintenance of postoperative analgesia
- Lower total cost per procedure

*In a comparative study[1,2] of patients undergoing major orthopedic surgery who received either SUFENTA-N_2O (n=10) or isoflurane-N_2O (n=10).

1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

COMPARED WITH FENTANYL[3,4]

- Smoother, more rapid induction
- Smoother, more stable intraoperative course
- Faster, more comfortable recovery
- More effective blocking of surgical stress response
- Superior hemodynamic stability
- Smaller volume of injection
- Lower total cost per procedure

3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.
4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

For complete Product Information, please see next page. JPI-514

world leader in anesthesia research

JANSSEN
PHARMACEUTICA

SUFENTA®
(sufentanil citrate) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be ⅕-⅐ those of fentanyl on a mg/kg basis.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 µg/kg in the maintenance of balanced general anesthesia

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD$_{50}$ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:
Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD$_{50}$ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD$_{50}$s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
1-2 µg/kg: administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
2-8 µg/kg: administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**25-50 µg (0.5-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 µg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 µg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 µg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 µg/ml, 5 ml ampoules in packages of 10

Protect from light. Store at room temperature.

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854

7618500

U.S. Patent No. 3,998,834
May 1984

Introducing STRAPEZE™

While others slip and slide all over the place, we've made a name for ourselves by staying put.

No more fumbling for the tape. No more sticky adhesive devices. And no more concerns for the security and safety of your patient's airway. Now enjoy the speed, simplicity and protection of STRAPEZE.

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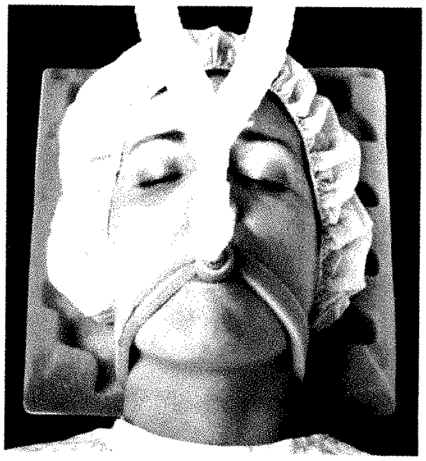
Tape kinks, binds, and often loses its adhesive qualities under operating conditions. STRAPEZE, as its name implies, is a strap made of 100% non-allergenic Velfoam II®, a very durable and lightweight material with a foam core sandwiched between outer layers of soft, synthetic lambs-wool.

So easy to apply

The STRAPEZE "one-step" fastening concept brings a new measure of assurance and security to endotracheal tube placement. And there's nothing else like it for ease of use. You simply attach one end of STRAPEZE to the tube, slip the strap behind the patient's neck, loop around tube and fasten with the Velcro tab back onto the strap's velvety surface. Job finished!



Stays put—or it's not STRAPEZE!

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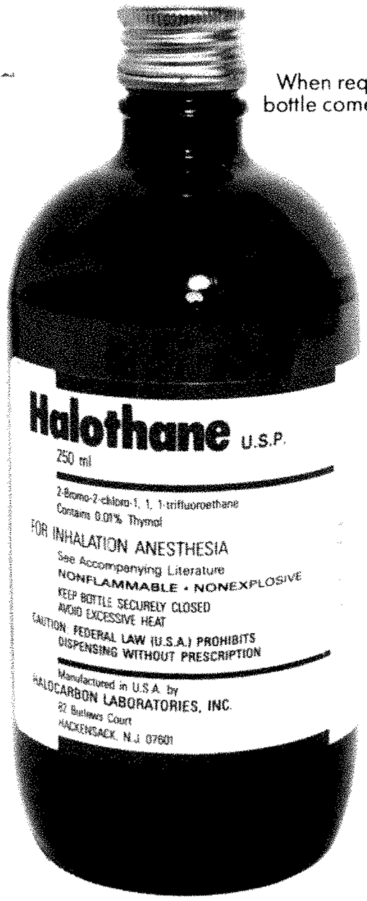

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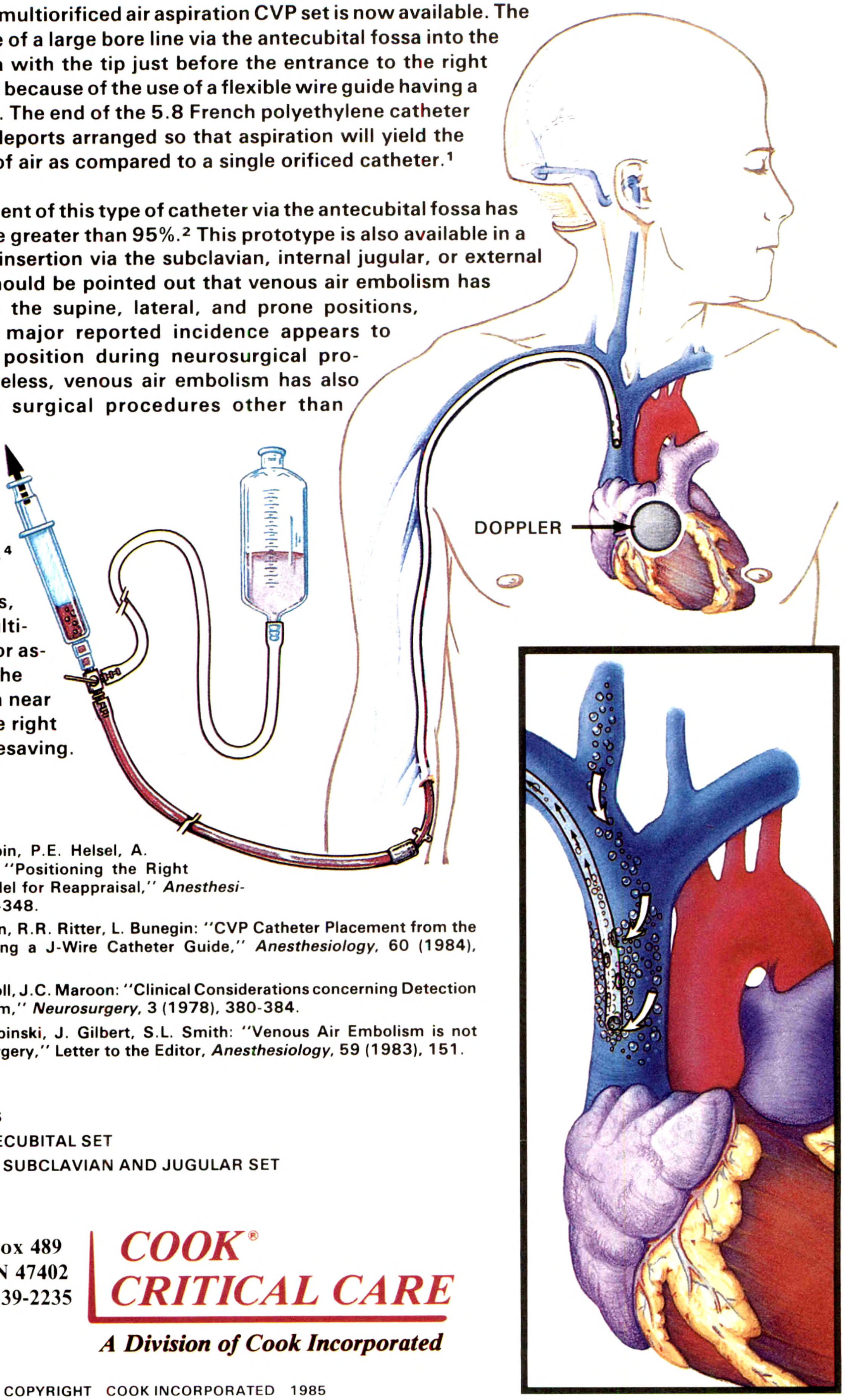

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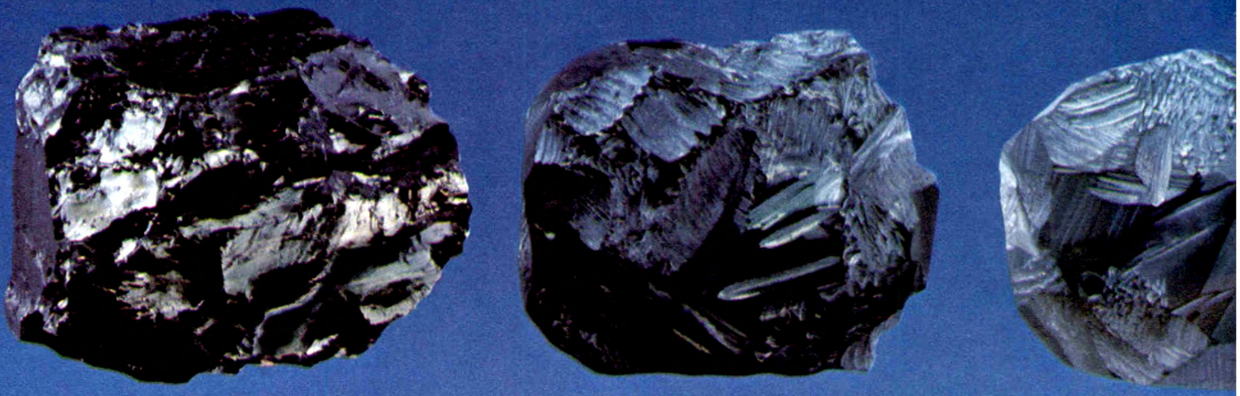

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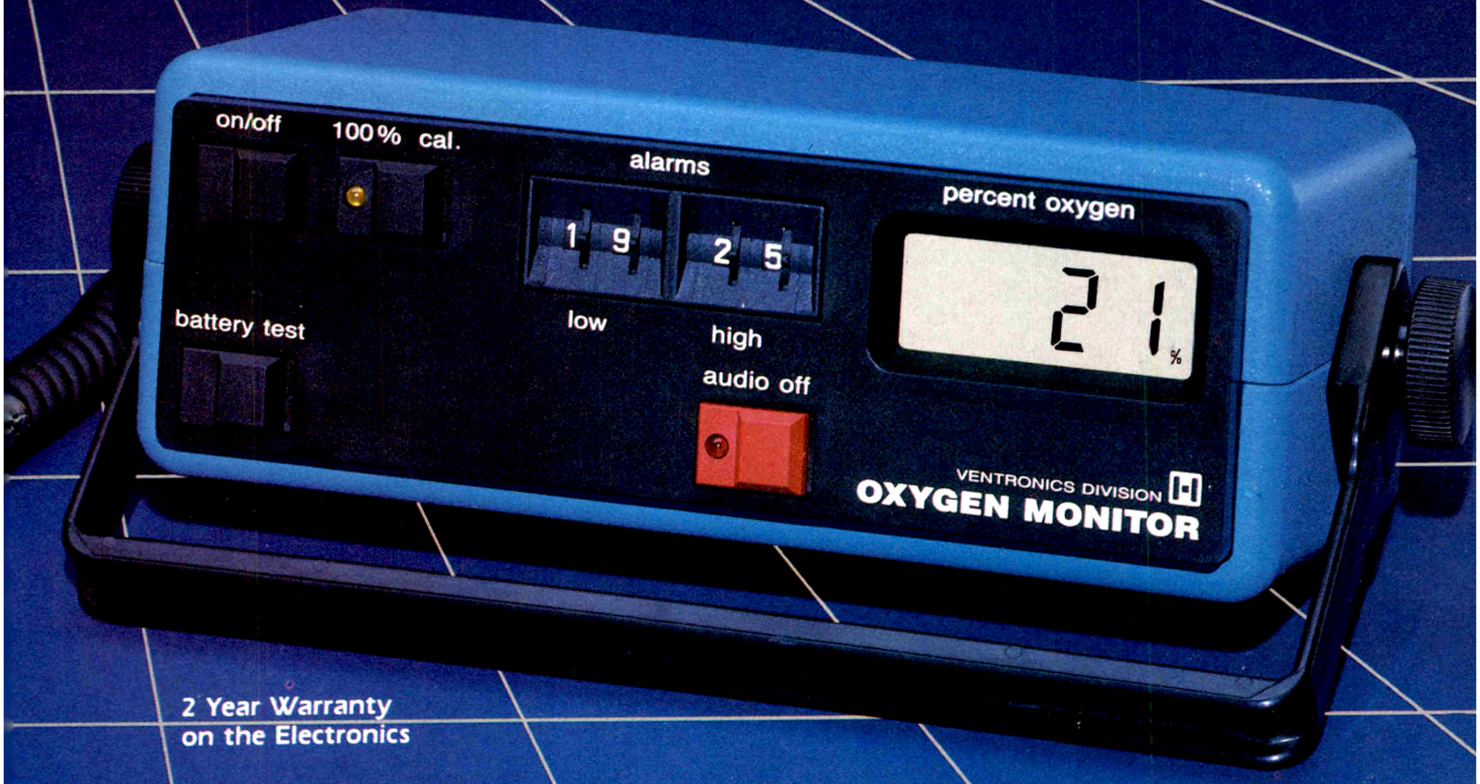

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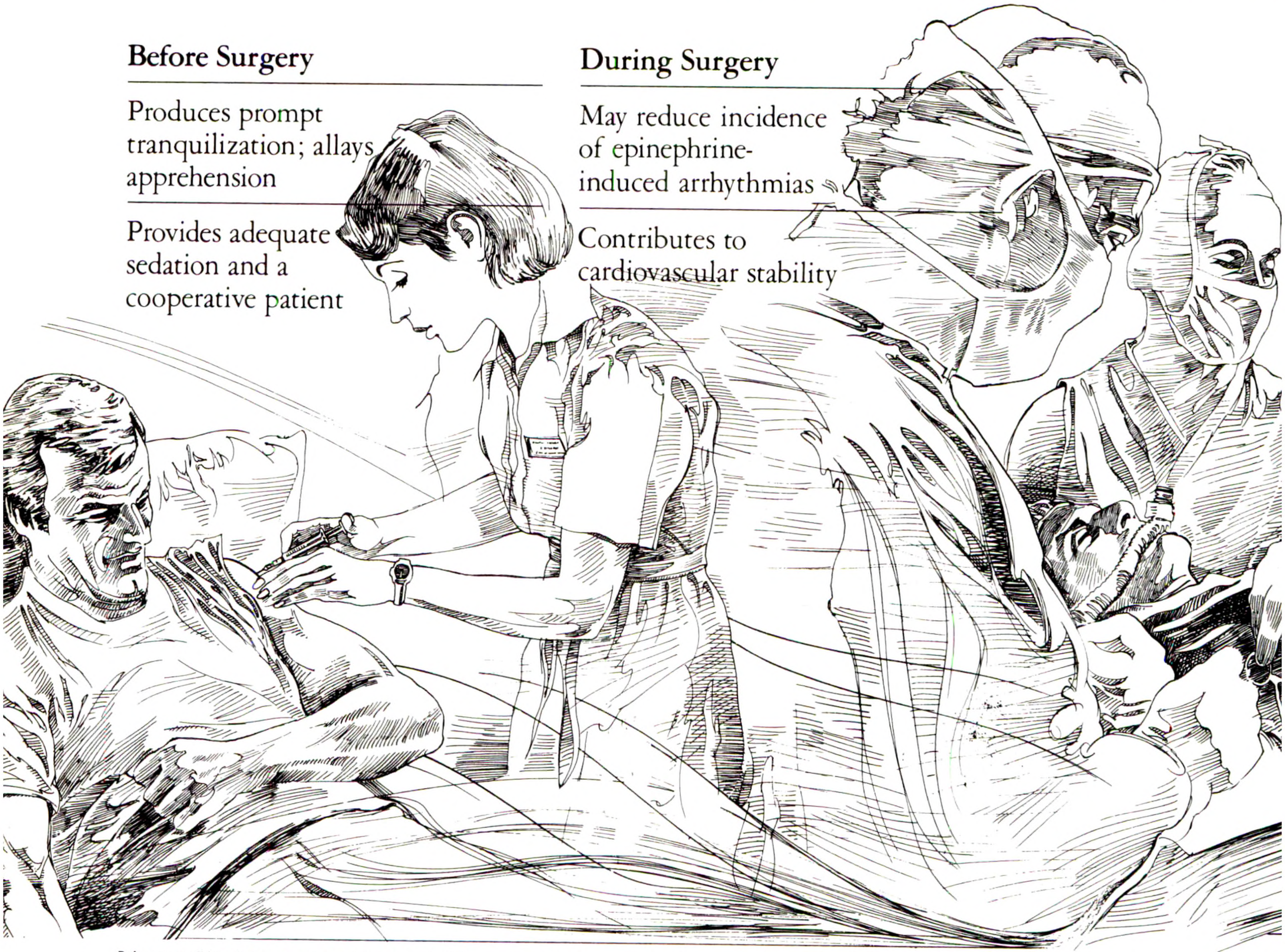

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INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

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Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur.

Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
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III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

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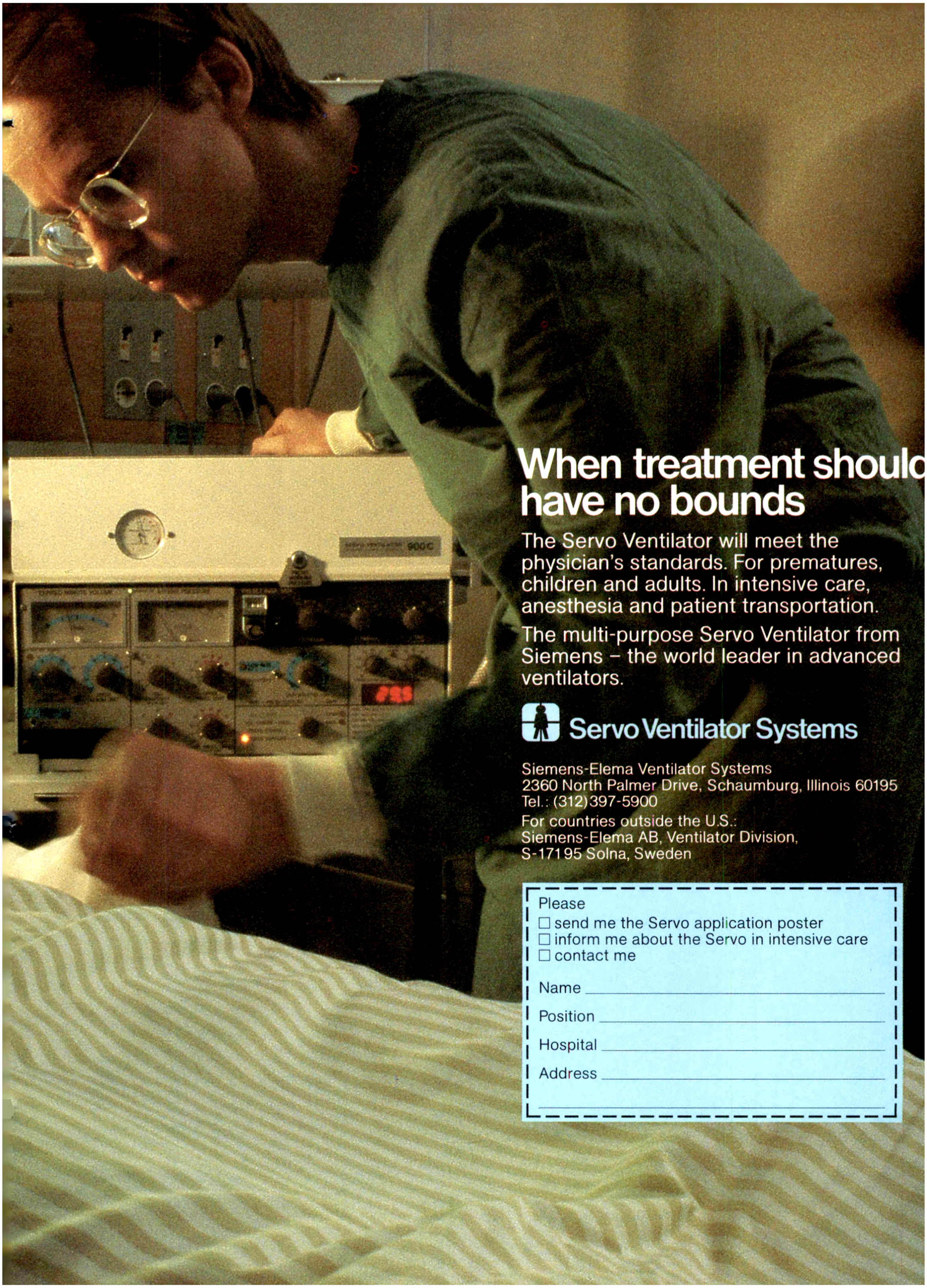

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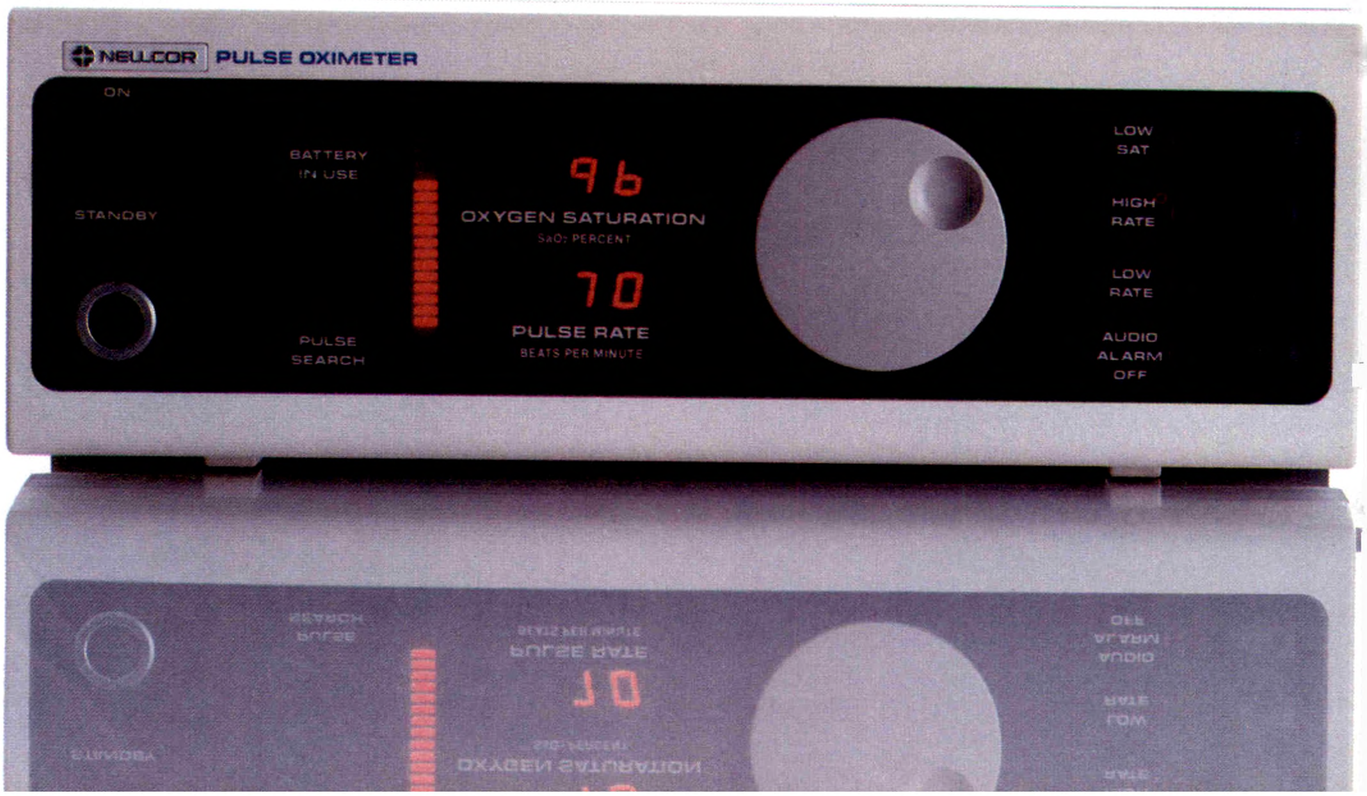

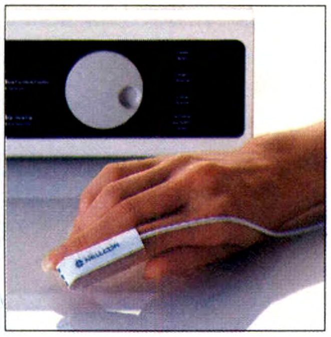

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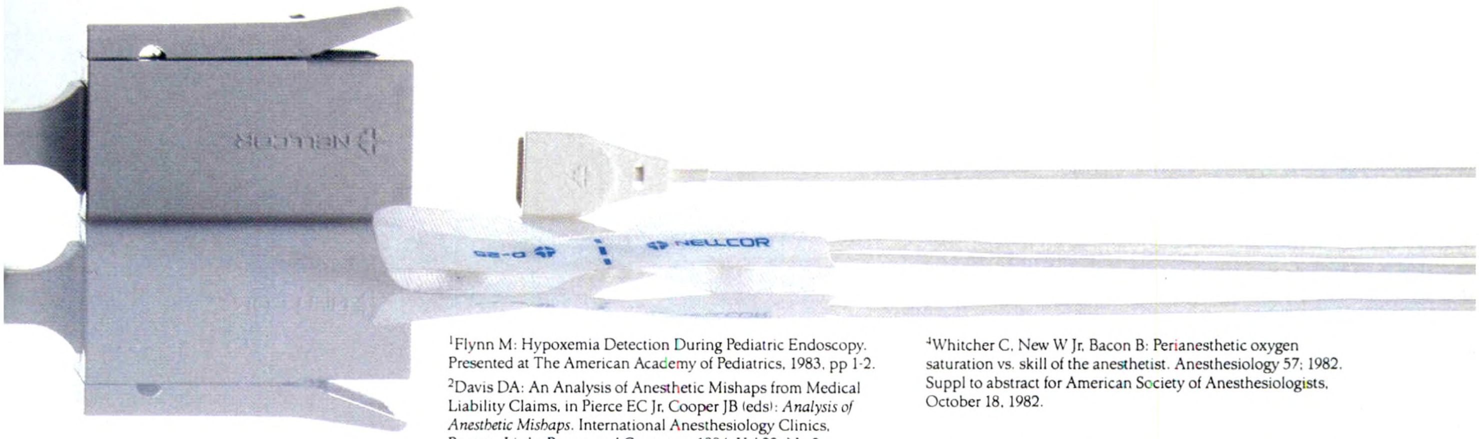

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THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Local-anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection—intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types; severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended.

Mixing, or a prior or intercurrent use, of any other local anesthetic with MARCAINE cannot be recommended because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

PRECAUTIONS: General: Safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have I.V. fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

Epidural Anesthesia: The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. During an epidural procedure, it is recommended that a test dose be administered initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. Clinical conditions permitting, the test dose should contain epinephrine (10-15 μg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect unintended intrathecal injection. This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or, in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 μg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart block.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response; ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use these agents concurrently, their combined action on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduction are potentially triggering agents for familial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene I.V. (see prescribing information before use), and other supportive measures.

Use in Head and Neck Area: Small doses of local anesthetics injected into the area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported and may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored constantly, with resuscitative equipment and personnel immediately available if needed. Do not exceed dosage recommendations. (See DOSAGE AND ADMINISTRATION.)

Use in Ophthalmic Surgery: With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

Use in Dentistry: Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa; advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

Information for Patients: When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or other possible adverse occurrence noted in package insert.

Clinically Significant Drug Interactions: Administering local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided; in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

(continued on next page)

Marcaine® HCl

(bupivacaine HCl injection, USP) with or without epinephrine 1 200,000

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)

Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.

Nursing Mothers: It is not known whether local anesthetics are excreted in human milk; because many drugs are, administer with caution.

Pediatric Use: Without further experience in children under 12, MARCAINE is not recommended for this group.

ADVERSE REACTIONS: A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

Systemic: The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System: Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.

Cardiovascular: High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)

Allergic: Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.

Neurologic: Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug used, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinals are characterized by leg paralysis, loss of consciousness, respiratory paralysis, and bradycardia. Effects following epidural or caudal anesthesia may include: spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

OVERDOSAGE: Acute emergency during therapeutic local anesthesia is generally related to high plasma levels or unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. *The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of* ***immediate*** *attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus I.V. injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg I.V. bolus of diazepam, or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS, respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of I.V. fluids and, when appropriate, a vasopressor dictated by the clinical situation (eg, ephedrine or epinephrine to enhance myocardial contractile force).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis; with bupivacaine, within a minute of onset. These observations suggest that O_2 consumption and CO_2 production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen; if not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur; underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous in pregnant women. The parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished. (See Labor and Delivery in PRECAUTIONS.)

Composition of Marcaine Solutions: 0.25%—each mL contains 2.5 mg bupivacaine; 0.5%—each mL contains 5 mg bupivacaine; 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple-dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothioglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium

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ANESTHESIOLOGY

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ANESTH ANALG
1985;64:305–11

Assessment of β-Adrenoceptor Blockade during Anesthesia in Humans:

Use of Isoproterenol Dose–Response Curves

J. Dagnino, MD, and C. Prys-Roberts, DM, PhD, FFARCS

DAGNINO J, PRYS-ROBERTS C. Assessment of β-adrenoceptor blockade during anesthesia: use of isoproterenol dose–response curves. Anesth Analg 1985;64:305–11.

Patients with hypertension or ischemic heart disease are often treated with β-adrenoceptor antagonists, yet the degree of β-adrenoceptor blockade has rarely been studied in relation to anesthesia. We have constructed isoproterenol dose–response curves in four groups of patients under general anesthesia: group I, 27 elderly normotensive patients not receiving drugs; group II, 14 hypertensive patients treated with cardioselective β-adrenoceptor antagonists; group III, 15 hypertensive patients receiving nonselective β-adrenoceptor antagonists; group IV, 13 patients receiving an infusion of labetalol at 0.15 $mg \cdot kg^{-1} \cdot hr^{-1}$. Geometric mean CD_{25}, the dose of isoproterenol required to increase the heart rate by 25 beats/min was 4.4 μg (3.5–5.6, 95% confidence interval (CI) of the mean) in group I, and 27 μg (19–38, 95% CI), 39 μg (29–52, 95% CI), and 95 μg (62–147, 95% CI) in groups II, III, and IV, respectively. All differences were significant ($P < 0.01$), except those between groups II and III ($P < 0.1$). No signs of myocardial ischemia and only a few transient arrhythmias were observed. Isoproterenol dose–response curves are a safe means to assess the degree of β-adrenoceptor blockade during anesthesia and the postoperative period.

Key Words: HEART—β-adrenoceptor blockade. SYMPATHETIC NERVOUS SYSTEM—β-adrenoceptor blockade. ANESTHESIA—cardiovascular.

An increasing number of patients whose hypertension, ischemic heart disease, or both are treated with β-adrenoceptor antagonists are presenting for anesthesia and surgery. There is ample evidence that adequate β-adrenoceptor blockade will protect the cardiovascular system of these patients from undue increases in myocardial work and oxygen consumption caused by sympathetic overactivity occurring before (1), during (2–4), and after surgery (5). Although there is consensus in maintaining therapy with β-adrenoceptor antagonists in surgical patients (6–8), there is still considerable controversy and uncertainty on the timing of the last dose before surgery, and especially on the postoperative management of these patients (9).

The quantitative assessment of β-adrenoceptor blockade is, therefore, of considerable clinical importance. Among the various methods described for this assessment (10), only the isoproterenol sensitivity test is suitable for use during anesthesia and the postoperative period, and it has been advocated as a means of guiding therapy with β-adrenoceptor antagonists in this context (3,11,12). Many studies of isoproterenol sensitivity have shown that the heart rate response to isoproterenol is influenced by age (13–15), hypertension (16–18), and the type of β-adrenoceptor agent (19,20). Most patients taking β-adrenoceptor antagonists for the treatment of hypertension or ischemic heart disease are older than 45 yr, yet we have found no adequate studies that quantitate isoproterenol sensitivity in such elderly patients. These are necessary to provide a baseline for pharmacodynamic studies of β-adrenoceptor blockade in the elderly patient. We have, therefore, determined the dose–response curves to intravenous bolus doses of isoproterenol in four groups of patients, awake and under general anesthesia, and compared these results with those obtained in young unanesthetized volunteers (13).

This study was supported in part by The British Council and The Wellcome Trust. Dr. Dagnino is assistant professor at the Catholic University, Santiago, Chile.

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Address correspondence to Dr. Prys-Roberts, Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW, United Kingdom.

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Methods

Sixty-nine patients, whose medical and anthropometric data are shown in Table 1, were divided into four groups.

Group I (n = 27) is comprised of elderly (47–75 yr) normotensive patients not receiving any drug therapy.

Group II (n = 14) is comprised of hypertensive patients treated with a cardioselective β-adrenoceptor antagonist; 11 patients were receiving atenolol (Tenormin; 100 mg/day), 2 patients were receiving metoprolol (Lopresor; 50 mg/day), and one patient was receiving 400 mg/day of acebutolol (Sectral).

Group III (n = 15) is comprised of hypertensive patients being treated with nonselective β-adrenoceptor antagonists; 11 patients were receiving 400–800 mg/day of labetalol (Trandate), 2 were receiving oxprenolol (Trasicor; 160 and 240 mg/day), respectively, and two patients were receiving (80 and 120 mg/day, respectively) propranolol (Inderal).

Group IV (n = 13) is comprised of patients receiving a labetalol infusion at 0.15 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ for induced hypotension or replacement therapy.

Most patients received the last dose of their usual β-adrenoceptor antagonist within 2 hr of anesthesia, and most patients underwent major vascular or abdominal surgery under a standardized anesthetic technique. Induction was achieved with fentanyl (2–10 $\mu\text{g}\cdot\text{kg}^{-1}$), sodium thiopental (2–4 $\text{mg}\cdot\text{kg}^{-1}$) or Althesin (2–4 ml), and pancuronium (0.08 $\text{mg}\cdot\text{kg}^{-1}$). Anesthesia was maintained in all cases with N_2O (67%) and O_2 (33%), and two-thirds of the patients received halothane (0.5–1%). Ventilation was controlled (Penlon, Oxford Ventilator) using a circle system without CO_2 absorber, and normal end-tidal carbon dioxide concentration was maintained by adjusting the fresh gas flows. Approval from the District Ethical Committee and informed consent were obtained.

Isoproterenol Sensitivity Test

The method followed was that described previously by Cleaveland et al. (13). The peak increase in heart rate, from a consistent resting value for each patient, was measured in response to at least four graded intravenous bolus injections of isoproterenol sulfate. The initial dose was 0.2 μg in the normotensive patients and 1 μg in patients receiving β-adrenoceptor antagonists. The dose was then progressively increased until the heart rate had increased by 25 beats/min or little more. Heart rate was allowed to return to baseline before subsequent doses of isoproterenol were given. Individual log dose–response curves were then constructed, and the dose of isoproterenol required to increase the heart rate by 25 beat/min, the chronotropic dose 25 (CD_{25}), was determined by interpolation. The CD_{25} was always positioned on the lower part of the straight central section of the sigmoid dose–response curve. When two or more dose–response curves were obtained in the same patient, the mean values were taken. The heart rate changes were computed electronically by means of an R-wave triggered instantaneous rate meter (Devices 4522). The ECG, with leads in a CM5 configuration, was continuously displayed on a Hewlett-Packard 78304A amplifier and signs of myocardial ischemia or arrhythmias were sought for and recorded. The ECG and instantaneous heart rate were continuously recorded by a Mingograph 81 (Elema-Schonander) ink-jet recorder.

Table 1. Anthropometric and Medical Data of the Four Groups

	Group I	Group II	Group III	Group IV
n	27	14	15	13
Age (yr ± SD)	62 ± 8	59 ± 7	59 ± 10	56 ± 10
Weight (kg ± SD)	66 ± 12	69 ± 10	69 ± 15	70 ± 14
IHD[a]	4	7	6	5

[a] Patients with ischemic heart disease evidenced by angina or previous myocardial infarction.

In 32 patients (15 elderly normotensives, 10 patients receiving a cardioselective β-adrenoceptor antagonist, and 7 patients receiving a nonselective β-adrenoceptor antagonist), the direct arterial pressure changes, measured through a brachial artery cannula connected to a P23ID Gould-Statham transducer and to the Hewlett-Packard amplifier, were recorded during the isoproterenol dose–response studies.

In 13 patients (6 elderly normotensives and 7 patients receiving a cardioselective β-adrenoceptor antagonist), isoproterenol dose–response curves were performed just before induction of anesthesia and then repeated during steady-state anesthesia. In 11 patients two, and in 5 patients three, isoproterenol dose–response curves were repeated during anesthesia to assess individual variability.

Statistics

A two-way analysis of variance and unpaired Student's t-tests were used on the log-transformed CD_{25} to compare groups. A similar analysis, with paired and unpaired Student's t-tests, was used to assess blood pressure changes. Bonferroni's transformation for multiple comparisons was used to control the error rate (21). Linear regressions were done using the least squares method.

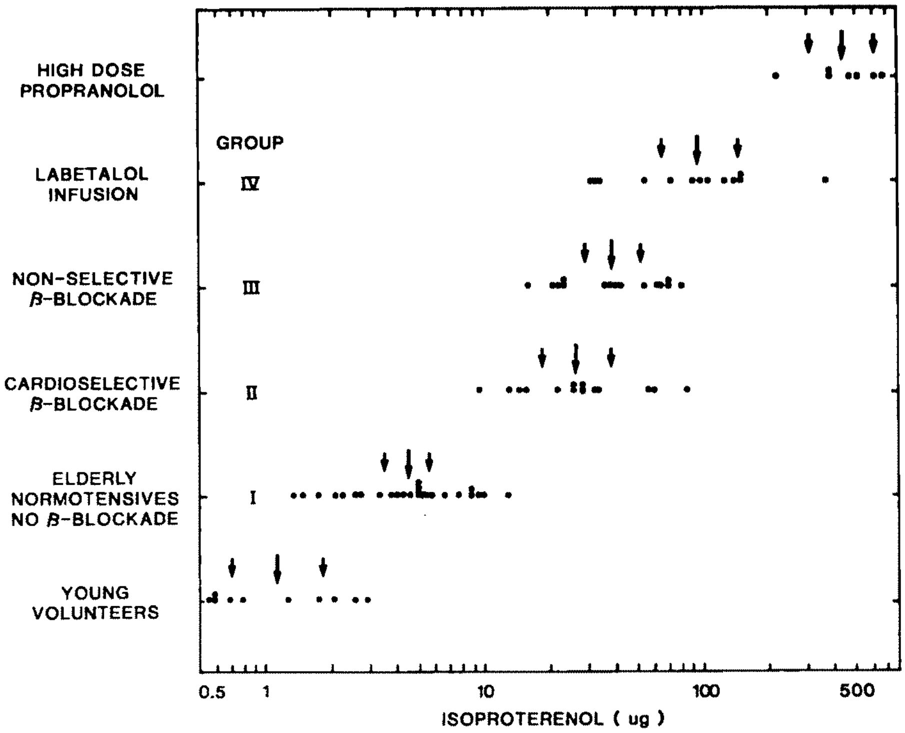

Figure 1. Distribution of the isoproterenol sulfate doses that induced a heart rate increase of 25 beats/min (CD_{25}) in the four groups. Isoproterenol sulfate equivalents of the data obtained by Cleaveland et al. (13) in young volunteers and those obtained by Prys-Roberts (3) in renovascular hypertensives receiving very high doses of propranolol are included for comparison. Arrows indicate the geometric mean and the 95% confidence intervals of the mean. All differences are significant ($P < 0.01$) except that between groups II and III ($P < 0.1$).

Results

Figure 1 and Table 2 show the distribution of the CD_{25} in the four groups, expressed as geometric means and 95% confidence intervals of the mean, demonstrating the wide and skewed intersubject variability. Figure 2 shows the averaged dose–response curves for each group. The data obtained by Cleaveland et al. (13) in young volunteers and those of Prys-Roberts (3), obtained in renovascular hypertensives receiving very high doses of propranolol, are included for comparison. All differences are significant ($P < 0.01$) except that between groups II and III ($P < 0.1$).

The overall variation for the CD_{25} in the same individuals was 18.7% and was similar in patients with or without β-adrenoceptor blockade.

In the six elderly normotensives, the geometric mean CD_{25} obtained before induction was 5 μg (3.74–6.26 μg, 95% CI), and that obtained under anesthesia was 6.3 μg (4.85–7.72, 95% CI). In the seven patients receiving cardioselective β-adrenoceptor antagonists these values were 27.7 μg (26–29.4 μg, 95% CI) and 26.6 μg (24.8–28.3, 95% CI), respectively. Both differences were statistically insignificant.

There was a significant decrease of systolic and diastolic arterial pressure in response to the CD_{25} dose of isoproterenol in the normotensive patients and in patients receiving a cardioselective β-adrenoceptor antagonist (Fig. 3). The mean decrease was 18% for systolic and diastolic pressures in the normotensives and 17% for systolic and 23% for diastolic arterial pressure in group II patients. By contrast, there was no significant change in either systolic or diastolic pressure in patients receiving a nonselective β-adrenoceptor antagonist (groups III and IV).

Table 2. Dose in μg of Isoproterenol Sulfate that Produced an Increase in Heart Rate of 25 beats/min (CD_{25})

Group I	Elderly normotensives	4.41	(3.49–5.57)
Group II	Cardioselective blockade	27	(19–38)
Group III	Nonselective blockade	39	(29–52)
Group IV	Labetalol infusions	95	(62–147)

Values are geometric means and (95% confidence intervals of the mean). All differences are significant ($P < 0.01$) except that between groups II and III ($P < 0.1$). For comparison 1 μg of isoproterenol sulfate is equivalent to 0.89 μg of isoproterenol hydrochloride and contains 0.758 μg of isoproterenol base.

Transient arrhythmias were observed in 9 of the 69 patients. Six of these were observed in group I patients and only three in patients receiving β-adrenoceptor antagonists. In six cases they were isolated ventricular ectopic beats, in two cases junctional tachycardias, and in one case a combination of both. Isolated ventricular ectopic beats were observed in one of the patients treated with a β-adrenoceptor antagonist while he was receiving 1% halothane, but did not occur again when the isoproterenol dose–response curve was repeated while under 0.5% halothane. No electrocardiographic signs of myocardial

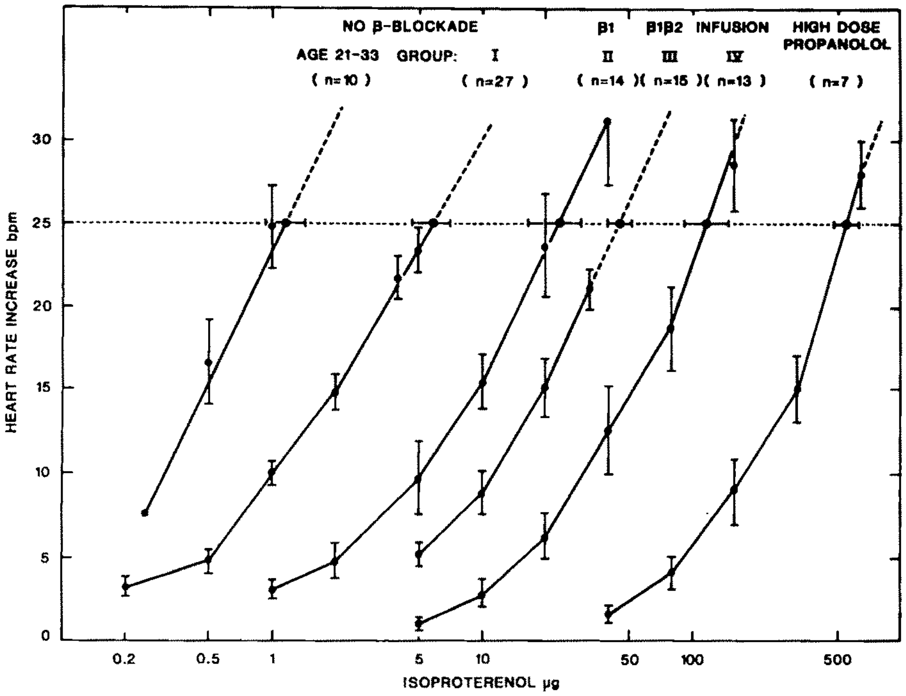

Figure 2. Averaged isoproterenol dose–response curves for the four groups included in the present study, together with data from young volunteers (age 21–33 yr) in Cleaveland et al. (13) and high dose propranolol patients from Prys-Roberts (3). Mean values ± SD are shown for each point.

ischemia were observed. No correlation was found between the CD_{25} and age, sex, weight, initial heart rate, or blood pressure.

Discussion

Considering how many patients presenting for anesthesia and surgery are receiving β-adrenoceptor antagonists as part of their medical therapy, very little attention has been paid to defining the extent of their β-adrenoceptor blockade before, during, and after anesthesia. Although isoproterenol dose–response curves have been used to define the agonist–antagonist interaction since the introduction of β-adrenoceptor antagonists and have been applied extensively in pharmacology and clinical medicine, their application in anesthesia has been limited (3,11). Nevertheless there is a great need for a method that can quantitate the state of β-adrenoceptor blockade, not only during anesthesia but also during the postoperative management of patients who cannot absorb drugs taken by mouth.

Although a rapid resting heart rate may, by implication, indicate inadequate β-adrenoceptor blockade, a slow resting heart rate does not necessarily imply adequacy. A number of other factors, related to disease states and their drug therapy, can be associated with slow heart rates in the absence of any β-adrenoceptor blockade. Heart rates below 50 beats/min are not uncommon in patients with mild untreated hypertension, and also in patients under therapy with cardiac glycosides, verapamil, and a number of antihypertensive drugs other than the β-adrenoceptor antagonists. Cardiologists and physicians commonly evaluate the adequacy of β-adrenoceptor therapy by exercise testing their patients, but this is not practical during anesthesia or in the intensive care unit.

Having previously used the isoproterenol dose–response as a means of quantifying β-adrenoceptor blockade in experimental animals (11) and in patients undergoing surgery during therapy with huge doses of propranolol (3), we have sought to establish the value of this test in determining the degree of β-adrenoceptor blockade in patients presenting for anesthesia. Many of these patients receive their drugs on the morning of proposed surgery, whereas others may have received their last dose on the evening before surgery. Depending on the pharmacokinetic profile of the β-adrenoceptor antagonist, prediction of the adequacy of β-adrenoceptor blockade is difficult. A further complication has been the relative lack of data on the response of elderly normotensive patients to isoproterenol.

The results of this study show that the isoproterenol sensitivity test is safe, simple, and the only one suitable for use during anesthesia and the postoperative period. We have shown that data obtained in young patients or volunteers cannot be used as the baseline standard for the response of the older patient

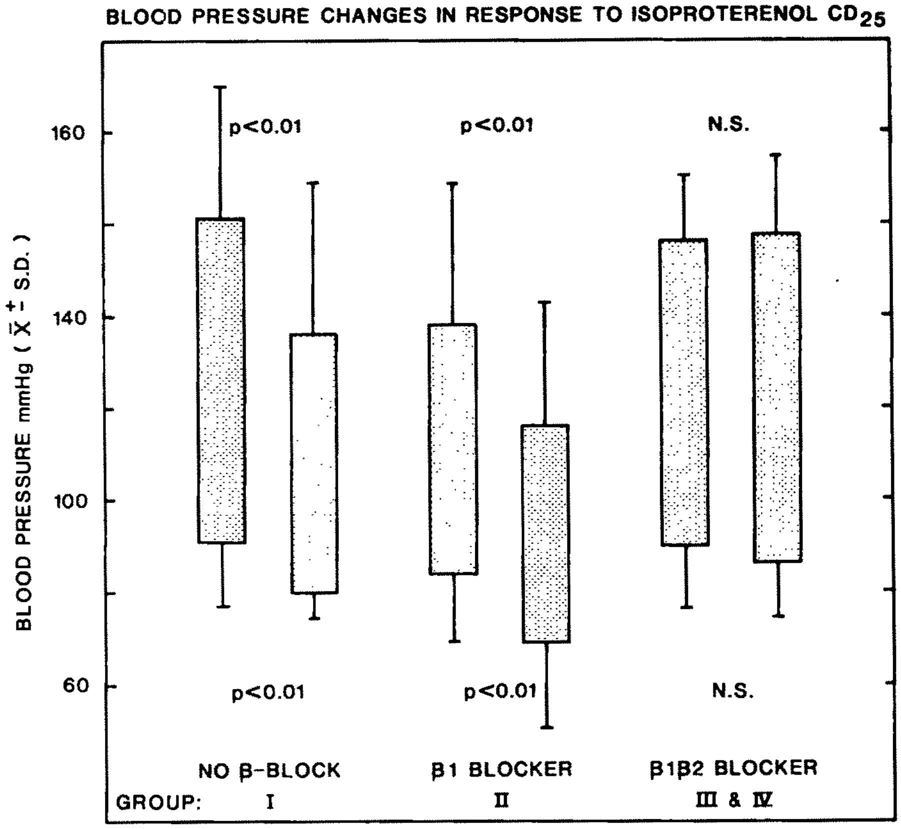

Figure 3. Direct systolic and diastolic arterial pressure changes (represented by the hatched columns, mean ± SD) in response to the CD$_{25}$ dose of isoproterenol sulfate. Elderly normotensive patients taking no β-adrenoceptor antagonists, and those taking cardioselective β_1-adrenoceptor antagonists are shown in the two leftmost pairs. Patients receiving nonselective $\beta_1\beta_2$-adrenoceptor antagonists (groups III and IV) are shown in the right pair.

taking β-adrenoceptor antagonists for the treatment of hypertension or ischemic heart disease. Although we have found wide intersubject variability as expressed in the range of CD$_{25}$ values determined in each group, the overlap between blocked and unblocked patients (Fig. 1) was minimal. In a separate publication (22) we have been able to correlate the CD$_{25}$ with plasma concentrations of labetalol or atenolol during infusions of these drugs. We can therefore confirm the validity of this test as a pharmacodynamic tool for the anesthesiologist. The variability of response of the individual patient was much better than that of each group in that our within-patient variability of CD$_{25}$ was 18.7%, a value similar to that determined by others (13,23).

The heart rate response to isoproterenol has two components. The first and most important one is the direct effect of the agonist on β_1 adrenoceptors in the heart. The second is indirect, a reflex vagal withdrawal secondary to the decrease in arterial pressure caused by the stimulation of β_2 adrenoceptors in peripheral blood vessels (24). This fact is of major importance for the interpretation of isoproterenol dose–response curves, and in their use for the assessment of β-adrenoceptor blockade, because factors that produce alterations of the baroreflex component can modify the heart rate response to isoproterenol without necessarily meaning a different degree of β-adrenoceptor sensitivity. Failure to recognize this fact could lead to confusion in the interpretation of results.

Isoproterenol sensitivity decreases with age (13–15). A true decrease in the β_1-adrenoceptor mediated response (15,25) is at least partially responsible for this correlation, but the decrease in baroreceptor responsiveness with advancing age (26) is probably as important. Decreased β-adrenoceptor affinity for agonists has also been demonstrated in leukocytes from elderly patients (27). We did not find a correlation between age and the CD$_{25}$ within our group of elderly normotensives. This could be due to the fact that we examined a narrow age band at only one end of the age range, but it could also mean that vagal withdrawal is only important in the younger age groups with intact baroreflex responses. This is supported by the fact that, although anesthesia significantly depresses baroreflex activity in humans (28), we found no difference between the awake and anesthetized isoproterenol sensitivity in our group of elderly normotensives.

Another factor that alters the response to isoproterenol is hypertension (15–18). The difference in CD$_{25}$ between normotensive and hypertensive patients has been shown to be due mainly to the decreased baroreceptor sensitivity seen in the latter (26), because it disappears when isoproterenol dose–response curves are repeated after autonomic blockade with atropine and clonidine (18).

The contribution of vagal withdrawal to the heart rate response to isoproterenol is also evidenced when patients receiving selective or nonselective β-adrenoceptor antagonists are compared (20,29). At doses judged to be equipotent by exercise testing, propranolol, a nonselective β-adrenoceptor antagonist, produced a greater displacement to the right of the isoproterenol dose–response curve than the cardioselective β-adrenoceptor antagonist practolol. The difference between the CD_{25} was found to be tenfold, but a fourfold difference still persisted after blockade with atropine. This fact probably means that other factors, still unidentified, as well as reflex vagal withdrawal, are responsible for the difference in isoproterenol sensitivity between the two types of β-adrenoceptor antagonists.

We found little difference between the CD_{25} values for our groups of patients treated with cardioselective or nonselective antagonists, despite the fact that all these patients were hypertensive and that all tests were done under anesthesia so that the contribution of vagal withdrawal was probably negligible. As the β-adrenoceptor doses in our patients were those clinically determined to be effective, this could mean that the nonselective agents produce their antihypertensive effect at lower degrees of β-adrenoceptor blockade than their selective counterparts. Alternatively, it could reflect the α-adrenergic blocking action of labetalol, because most patients in group III were being treated with this drug.

It has been argued that the isoproterenol sensitivity test is contraindicated in patients with ischemic heart disease because of the danger of inducing myocardial ischemia or arrhythmias (30). Yet with careful monitoring and limiting of the dose of isoproterenol to produce increases in heart rate of 25 beats/min, or little more, we found no evidence of myocardial ischemia and only a few transient arrhythmias after more than 250 injections of isoproterenol. It must be stressed that nearly half of the patients receiving β-adrenoceptor antagonists had evident ischemic heart disease. Responses to graded exercise, widely accepted in cardiological practice, frequently involve heart rate increases up to 130–140 beats/min (31), and usual end-points for the test include signs of myocardial ischemia and serious arrhythmias (32).

Probably the most important use of the isoproterenol test lies in the guidance of substitution therapy during the postoperative period in patients unable to receive their normal β-adrenoceptor antagonist orally (22). The wide differences in bioavailabilities between the different β-adrenoceptor antagonists and the fact that not all of them are obtainable in intravenous formulation make it very difficult to provide a rational therapy without monitoring the degree of β-adrenoceptor blockade.

We are grateful to Professor R.C.N. Williamson, and to Mr. R.N. Baird, Mr. D.J. Leaper, and Mr. N.J. Mortensen for permitting us to study patients under their care, and we are indebted to Mr. J. Dye for his invaluable technical assistance.

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Comparison of the Effects of 15 and 60 μg/kg Fentanyl Used for Induction of Anesthesia in Patients with Coronary Artery Disease

Michael G. Bazaral, MD, PhD, Reinhard Wagner, MD, Elie Abi-Nader, MD, and Fawzy G. Estafanous, MD

BAZARAL MG, WAGNER R, ABI-NADER E, ESTAFANOUS FG. Comparison of the effects of 15 and 60 μg/kg fentanyl used for induction of anesthesia in patients with coronary artery disease. Anesth Analg 1985;64:312–8.

We compared the effects of 15 and 60 μg/kg fentanyl used for induction in 40 patients, 50–72 yr old, with coronary artery disease and mildly impaired ventricular contractility. Morphine (0.1 mg/kg) and scopolamine (0.4 mg) were used for premedication. Crystalloid (500 ml) was administered before induction, and nitroglycerin (0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused during the study. Fentanyl, 15 or 60 μg/kg, was administered at a rate of 1.2 $\mu g \cdot kg^{-1} \cdot sec^{-1}$. Pancuronium (0.04 mg/kg) and metocurine (0.16 mg/kg) were used for muscle relaxation. Data were collected 2 min before induction (baseline), before intubation (3 min), at 6 min, and at 13 min. Responses to 15 and 60 μg/kg were similar. At 3 min the heart rate (HR) in patients given 15 μg/kg increased by 6; whereas the HR in those given 60 μg/kg increased by 14 ($P < 0.01$). Subsequent differences in HR were not significant. There were no dose-related differences in mean arterial pressure, cardiac index, central venous pressure, or pulmonary capillary wedge pressure. The EEG showed high-voltage low-frequency activity within 2 min in all patients. Arterial plasma fentanyl concentrations at 3 min averaged 25.9 ± 3.8 ng/ml with 15 μg/kg and 89.9 ± 15.2 ng/ml with 60 μg/kg. At 4 hr, plasma concentrations averaged 0.4 ± 0.2 ng/ml and 3.6 ± 0.7 ng/ml, respectively. We conclude that anesthesia for induction and intubation is achieved by the rapid administration of 15 μg/kg fentanyl and that 60 μg/kg has no substantially different effect on cardiovascular responses.

Key Words: ANESTHESIA—cardiovascular. ANESTHETICS, INTRAVENOUS—fentanyl.

Induction of anesthesia with fentanyl produces minimal effects on the heart and circulatory system. Alone or in combination with other agents, fentanyl suppresses hemodynamic responses to laryngoscopy and tracheal intubation. These properties permit anesthesia to be induced uneventfully in patients with cardiac disease.

Early studies with fentanyl were done using slow administration of the drug (1). It has since become evident that the protracted induction time required with morphine is not necessary with fentanyl because fentanyl causes little histamine release (2) and little vasodilation in comparison with morphine (3). Truncal rigidity and airway obstruction (4), which may occur with the rapid administration of fentanyl (5,6), can be eliminated by the administration of a muscle relaxant (7). Fentanyl appears to have a flat dose–response curve above 30 ng/ml serum concentration in animals (8), and in humans a wide range of serum levels is tolerated well (9,10). The purpose of this study was to ascertain whether the dose of fentanyl, above some lower limit, has an effect on the depth of anesthesia and on cardiovascular responses during induction and tracheal intubation.

The lower limit for the induction dose has not been defined, but 30 μg/kg appears to be as satisfactory as 60 μg/kg for induction and tracheal intubation (11). Average doses as low as 11–18 μg/kg (9) administered over several minutes have been used for induction of anesthesia in patients with coronary artery disease. More rapid administration produces transiently higher serum levels (10). Therefore, it seems likely that fixed doses of 15 μg/kg, administered rapidly, would provide satisfactory induction and anesthesia for tracheal intubation. However, there is limited experimental evidence to suggest that 15 μg/kg fentanyl alone is inadequate for induction (12) and that 50 μg/kg depresses cardiac output (13).

We compared rapidly administered doses of 15 μg/kg

Received from the Department of Cardiothoracic Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio. Accepted for publication October 24, 1984. Present address for Dr. Wagner is the Department of Anesthesiology, Mount Sinai Medical Center, Milwaukee, Wisconsin. Present address for Dr. Abi-Nader is the Department of Anesthesiology, St. Joseph's Hospital, Phoenix, Arizona.

Address correspondence to Dr. Bazaral, Department of Cardiothoracic Anesthesia, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44106.

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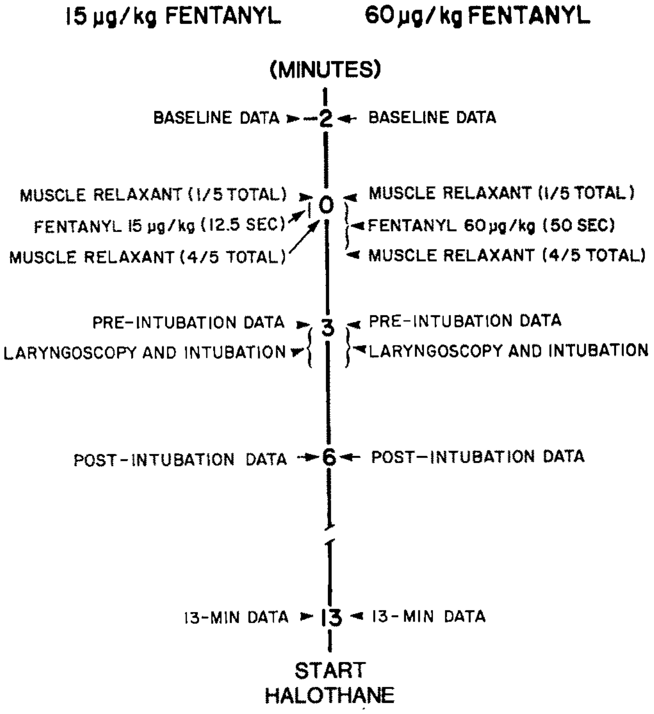
15 µg/kg FENTANYL
60 µg/kg FENTANYL
(MINUTES)
BASELINE DATA
-2
BASELINE DATA
MUSCLE RELAXANT (1/5 TOTAL)
0
MUSCLE RELAXANT (1/5 TOTAL)
FENTANYL 15 µg/kg (12.5 SEC)
FENTANYL 60 µg/kg (50 SEC)
MUSCLE RELAXANT (4/5 TOTAL)
MUSCLE RELAXANT (4/5 TOTAL)
PRE-INTUBATION DATA
3
PRE-INTUBATION DATA
LARYNGOSCOPY AND INTUBATION
LARYNGOSCOPY AND INTUBATION
POST-INTUBATION DATA
6
POST-INTUBATION DATA
13-MIN DATA
13
13-MIN DATA
START
HALOTHANE

Figure 1. Sequence of events during induction. Actual times for recording of hemodynamic data were within 20 sec of the times indicated. Samples for plasma fentanyl concentration were drawn concurrently with recording of hemodynamic data.

fentanyl with doses of 60 µg/kg. Hemodynamic and electroencephalographic responses, plasma fentanyl concentrations during induction and after tracheal intubation, and plasma fentanyl levels 4 hr after induction were measured.

Methods

Approval was obtained from the institutional committee on human research. Subjects were 40 patients of both sexes, 50–72 yr old, with arteriosclerotic coronary artery disease, who were scheduled for coronary artery bypass surgery. Patients who had severely impaired ventricular function, valvular disease, or systemic disease other than diabetes or hypertension were excluded. Patients who consented were alternately assigned to receive either 15 or 60 µg/kg fentanyl for induction of anesthesia. Left ventricular (LV) function was graded according to the cardiologist's evaluation of overall contractility demonstrated on the ventriculogram; 22 patients had normal contractility, 17 had mild impairment, and one had moderate impairment. Preoperative medical management included β-blocking agents (23 patients), calcium-channel blocking agents (11 patients), and long-acting nitrate or nitrite preparations (14 patients). Retrospective analysis showed no significant difference between the high-dose and low-dose groups with respect to either preoperative LV function or drug therapy. Preoperative medications were administered according to the patient's usual schedule until anesthetic premedication was given.

Table 1. Arterial Plasma Fentanyl Concentrations during and after Induction with 15 and 60 µg/kg Fentanyl

	Dose	
Time	15 µg/kg	60 µg/kg
−2 min	0.0 ± 0.0[a]	0.0 ± 0.0[a]
3 min	25.9 ± 3.8	89.8 ± 15.2
6 min	13.1 ± 2.1	36.9 ± 4.2
13 min	4.2 ± 1.6	23.0 ± 2.7
4 hr	0.4 ± 0.2	3.6 ± 0.7

[a] Mean plasma fentanyl concentration (ng/ml ± SEM); n = 10.

Patients were brought to the operating room 15–45 min after premedication with morphine sulfate (0.15 mg/kg), scopolamine hydrobromide (0.4 mg) intramuscularly and transcutaneous nitroglycerin (NTG; NitroDur, 5 mg). A radial arterial cannula, an intravenous cannula, and a thermistor-tipped flow-directed pulmonary artery catheter were placed percutaneously with the patient under local anesthesia. Monitoring included a V_6 ECG lead and a bipolar EEG lead (left frontal–mastoid). Administration of lactated Ringer's solution (500 ml over 10 min) was begun. Infusion of NTG (0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started and continued until after the last hemodynamic measurement. The operating room table was placed in a 5° head-down tilt. Induction was begun 5 min later. After preoxygenation for one min, one-fifth of a total muscle relaxant dose of 0.04 mg/kg pancuronium bromide and 0.16 mg/kg metocurine iodide was administered via a central venous port, followed immediately by fentanyl at a rate of 1.2 $\mu g \cdot kg^{-1} \cdot sec^{-1}$, and then by the remainder of the relaxant dose administered as a bolus. Positive pressure ventilation with oxygen via mask was begun when the patient became apneic. Laryngoscopy and placement of a cuffed orotracheal tube were begun 3 min after the start of fentanyl administration and were completed in 45 sec or less. Mechanical ventilation with oxygen at a rate of 10 breaths/min with a tidal volume of 8 ml/kg was then instituted. A urethral catheter and an orogastric tube were placed, and skin preparation was begun between 6 and 13 min after the beginning of fentanyl administration. After the last hemodynamic measurements for the study were made, 1% halothane was added to the inspired gas. The concentration of halothane was adjusted as required for maintenance of anesthesia.

Events were timed in relation to the start of fen-

Table 2. Hemodynamic Data during Induction of Anesthesia with 15 and 60 μg/kg Fentanyl

	Fentanyl dose (μg/kg)	Control	After induction	After intubation	Before incision
HR (beats/min)[a]	15	61 ± 12	67 ± 15	72 ± 20[b]	67 ± 14
	60	65 ± 11	79 ± 12[b,c,d]	81 ± 14[b]	74 ± 14[b]
MAP (torr)[a]	15	86 ± 15	74 ± 15[b]	88 ± 16	87 ± 15
	60	89 ± 18	82 ± 17	95 ± 20	94 ± 19
MPAP (torr)[a]	15	18 ± 5	17 ± 6	17 ± 6	17 ± 5
	60	17 ± 5	19 ± 7	20 ± 7	21 ± 6[b,c]
CVP (torr)[a]	15	6 ± 5	6 ± 4	7 ± 4[b]	8 ± 4[b]
	60	7 ± 3	8 ± 3	9 ± 3[b]	10 ± 3[b]
PCWP (torr)[a]	15	9 ± 4	10 ± 4	10 ± 4	11 ± 4
	60	11 ± 4	13 ± 5	13 ± 5	13 ± 4
CI (L·min^{-1}·m^{-2})	15	2.6 ± 0.5	2.5 ± 0.6	2.8 ± 0.9	2.6 ± 0.6
	60	2.8 ± 0.8	3.0 ± 0.7	3.2 ± 0.8	3.2 ± 0.7
SVR (dyne·sec·cm^{-5})[a]	15	1381 ± 377	1212 ± 348	1318 ± 407	1365 ± 403
	60	1226 ± 383	1020 ± 285[b]	1141 ± 337	1112 ± 310
LVSWI (g·m·m^{-2})[a]	15	45 ± 12	33 ± 11[b]	41 ± 14	41 ± 15
	60	46 ± 10	35 ± 11[b]	43 ± 11	46 ± 10

Values expressed as means ± SD.

[a] Denotes variables for which the measurements subsequent to the baseline measurements are different from baseline ($P < 0.001$).

[b] The value for this dose at the indicated time is significantly different from the corresponding baseline value ($P < 0.01$).

[c] The change from the baseline measurement with 60 μg/kg is significantly different from the change from the baseline measurement with 15 μg/kg ($P < 0.01$).

[d] The value for the group given 60 μg/kg is significantly different from the value for the group given 15 μg/kg ($P < 0.01$).

tanyl infusion (0 min). Hemodynamic data and blood samples were taken before fentanyl infusion (−2 min), just before tracheal intubation (3 min), after intubation (6 min), and at 13 min (Fig. 1). The timing of data collection and withdrawal of arterial blood samples was no more accurate than ± 20 sec because measurements and sampling using the same catheter were, of necessity, taken sequentially. Pressures were transduced (Bentley Trantec 800) with the zero referenced to 10 cm above the table at the fourth intercostal space. Waveforms were displayed on a 4-channel oscilloscope monitor (E for M model IM/OM-4), which also provided a digital display of mean pressures. A Gould cardiac output computer was used to derive cardiac output; thermodilution cardiac output measurements were performed in duplicate using 10 ml of room-temperature D5W. The cardiac output at each data point was taken to be the average of the duplicate measurements. The correlation coefficients between individual determinations constituting duplicates was 0.88. The EEG was continuously recorded and displayed in a processed and compressed form on a Neurometrics EEG computer. The EEG data were interpreted by comparison to reference patterns.

Arterial plasma samples for assays of fentanyl levels were stored in glass tubes at −20° until collection of patient data was completed. Radioimmunoassays were done using FEN-RIA-200 kits manufactured by the Institut National des Radioéléments (Belgium) using methods described by the manufacturer; the materials and methods for this assay are similar to those of Michiels et al. (14). Data from the 11 most recent patients in each group were reviewed. Technical problems occurred with one sample in each group; these values were discarded, leaving valid plasma concentrations for 10 patients in each group.

On the first or second day after surgery, patients were interviewed to evaluate recall. Patients were asked specifically whether they recalled the operating room, the anesthesia mask, or any subsequent event.

Statistical analysis was done using the BMDP program library (BMDP Statistical Software, Los Angeles, CA). For each variable, repeated-measures analysis of variance was used to examine differences between the two treatment groups and the four times. For variables having significant changes relative to the control values, Student's *t*-tests were done to assess specific differences between groups at each of the four times. The differences between high-dose and low-dose groups with respect to the changes from control were evaluated by paired *t*-test. In order to take the multiple testing into account, each test was considered significant only if the *P* value was less than 0.01. Correlation coefficients were computed using Pearson's product—moment formula; confidence intervals for correlation coefficients were computed using Fisher z values.

Results

Plasma fentanyl levels differed significantly in the groups given 15 and 60 μg/kg, initially corresponding to the difference in dose (Table 1). The plasma concentration immediately before intubation averaged 25.9 ± 3.8 ng/ml (± SEM) with 15 μg/kg and 89.8 ± 15.2 ng/ml with 60 μg/kg. Four hours later the average levels were 0.4 ± 0.2 ng/ml and 3.6 ± 0.7 ng/ml, respectively.

Hemodynamic data are shown in Table 2. Differences in baseline values between the groups were not significant. Relative to the baseline, there were significant changes at some point during induction in average values for heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), systemic vascular resistance (SVR), and left ventricular stroke work index (LVSWI) for one or both groups of patients. Changes in pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) were not significant.

The hemodynamic responses with 15 and 60 μg/kg were similar (Fig. 2). Three minutes after the start of induction, the average HR of the group given 15 μg/kg had increased by 6 beats/min, whereas the HR of the group given 60 μg/kg increased by 14 beats/min; this difference between groups is statistically significant (Table 2). Subsequent differences in HR between groups were smaller and not significant. At the last point, 13 min after the start of induction, the MPAP with 15 μg/kg had increased by 1 mm Hg, whereas the MPAP with 60 μg/kg increased by 4 mm Hg; the change from baseline MPAP was significantly greater with 60 μg/kg. There were no other significant differences between the groups given 15 or 60 μg/kg fentanyl.

Although average values of hemodynamic data during induction remained similar to baseline values, individual variation was considerable. Correlations between baseline and subsequent values as well as the absolute values were similar with both 15 and 60 μg/kg, and for simplicity the groups were pooled for the correlation data presented in Table 3. Correlation coefficients comparing baseline values with subsequent values for the same patient were between 0.6 and 0.8. The scatter plots for HR, MAP, and CI (Fig. 3) show postintubation values compared with baseline values and illustrate the changes in individual patients.

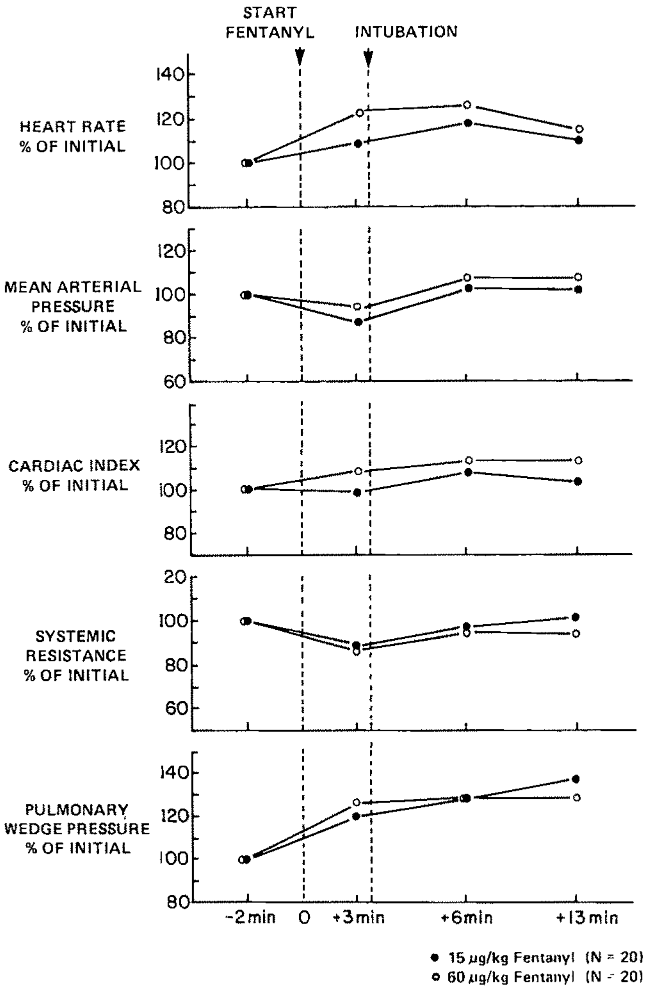

Figure 2. Hemodynamic changes during induction with 15 or 60 μg/kg fentanyl. Values are expressed as percentage of change of the average values relative to baseline values. Fentanyl infusion was begun at time 0; baseline values were measured 2 min earlier (−2 min). Laryngoscopy and intubation were performed immediately after the 3-min data point. Absolute values, standard errors, and the results of statistical analysis are listed in Table 2.

In all patients, the electrocardiogram remained unchanged except for an increase in sinus rate above control levels at each of the three times HR was recorded (3, 6, and 13 min after the start of fentanyl administration). The processed EEG changed from an awake pattern with predominant alpha activity to a pattern consistent with deep narcotic anesthesia (high voltage delta with little high-frequency activity) within 2 min after the beginning of induction. After the transition to a narcotic anesthesia pattern, there were no further changes in the EEG throughout the 13-min study period. Patient movement occasionally occurred within the first 3 min after the start of induction. The use of the muscle relaxants precluded movement after 3 min. There were no episodes of high-frequency high-amplitude EEG activity suggestive of cortical seizures.

No patients recalled events in the operating room subsequent to breathing through an anesthesia mask. Of 20 patients given 15 μg/kg of fentanyl, 6 did not recall preoperative events after arrival in the operating room, 12 recalled placement of percutaneous catheters, and 2 recalled the anesthesia mask. Of 20 patients given 60 μg/kg, 4 did not recall events occurring after arrival in the operating room, 8 recalled placement of percutaneous catheters, and 8 recalled the anesthesia mask. Differences in recall were not significant by χ^2 analysis. There were no anesthetic com-

Table 3. Correlation of Postinduction Hemodynamic Values with Preinduction Values

	After induction	After intubation	Before incision
HR (beats/min)	0.76 (0.52–0.89)[a]	0.77 (0.54–0.89)	0.77 (0.54–0.89)
MAP (torr)	0.73 (0.47–0.87)	0.77 (0.54–0.89)	0.75 (0.50–0.88)
MPAP (torr)	0.76 (0.52–0.89)	0.64 (0.33–0.83)	0.69 (0.41–0.85)
CVP (torr)	0.75 (0.50–0.88)	0.81 (0.61–0.91)	0.74 (0.49–0.88)
PCWP (torr)	0.72 (0.45–0.87)	0.66 (0.35–0.84)	0.69 (0.41–0.85)
CI ($L \cdot min^{-1} \cdot m^{-2}$)	0.62 (0.32–0.82)	0.66 (0.37–0.84)	0.60 (0.26–0.80)
SVR ($dyne \cdot sec \cdot cm^{-5}$)	0.73 (0.47–0.87)	0.80 (0.59–0.91)	0.62 (0.32–0.82)

[a] Correlation coefficient and 99% confidence interval.

plications, and all patients, except one who had a small pneumothorax, were discharged from the ICU on the first postoperative day.

Discussion

Our results demonstrate that there is little difference between 15 and 60 μg/kg doses of fentanyl for induction of anesthesia; the heart rate was transiently higher with 60 μg/kg than with 15 μg/kg fentanyl, and late in induction, the pulmonary artery pressure was higher in the group given 60 μg/kg doses. The differences in HR and MPAP were small and of little clinical importance. The use of a pancuronium bromide and metocurine iodide mixture at a dose twice the ED_{95} does have an effect on HR similar (15) to the changes observed in this study. Because the group given 60 μg/kg fentanyl received most of the relaxant mixture 30 sec later than the group given 15 μg/kg, it is possible that the design of our study contributed to the observed difference in HR between the groups.

Although stability of hemodynamic function is regarded as one of the characteristics of anesthetic induction with fentanyl, it should be noted that in a previous study (1), stability of the average values was shown. The values of hemodynamic parameters averaged over many patients may be relatively constant during induction, but changes in values for individual patients may be substantial. We found correlations of postinduction values with baseline values to be in the range of 0.6–0.8, consistent with acceptable hemodynamic stability in most cases. However, the values for individuals are seen to change from the baseline values more than would be anticipated from analysis of average values alone. The correlations of postinduction values with baseline measurements are least for cardiac index, and it is likely that the experimental error inherent in cardiac output measurements (16) contributed to the lower correlations.

The present results pertain to a specific set of clinical and experimental circumstances. The patients were premedicated and were at least 50 yr old. These two factors may facilitate the use of a low dose of anesthesic for induction. Also, ventricular function in our patients was not severely impaired, and this may minimize any deleterious effects caused by rapid administration of fentanyl. Patients were premedicated with nitroglycerin, and its administration was continued throughout the induction. All patients were given a 500-ml crystalloid infusion, and anesthesia was induced in a 5° head-down tilt, in an attempt to optimize preload during administration of NTG and fentanyl. The rationale for NTG administration was to minimize the risk of ischemic episodes occurring during the study period, and to avoid the need to administer additional drugs during the course of the study. However, it is unclear whether the administration of NTG and manipulation of preload were important.

From these data, we are unable to interpret the observed small changes in CVP, PCWP, and LVSWI. During induction, ventilation changes from spontaneous to controlled; and after intubation, airway resistance and the pattern of ventilation is further modified. Thus the mean intrathoracic pressure will vary during induction. It is clear from other studies that the effects of changes in intrathoracic pressure on cardiac filling cannot be assessed accurately by simultaneous measurement of intrathoracic and intravascular or intracardiac pressures (17).

The EEG monitor used in this study did not provide quantitative information. Qualitatively, with both 15 and 60 μg/kg doses, the EEG pattern was consistent with deep narcotic anesthesia (18,19) before intubation and throughout the 13-min study period. This suggests that anesthetic levels of fentanyl were present in the brain even with the 15 μg/kg dose. Reports of convulsions associated with fentanyl administration in patients in whom the EEG was not monitored (20,21) are of concern, but they are difficult to interpret because patient movement may occur during induction, as in our study, without EEG evidence of cortical seizures. A report based on extensive experience with EEG monitoring during induction of anes-

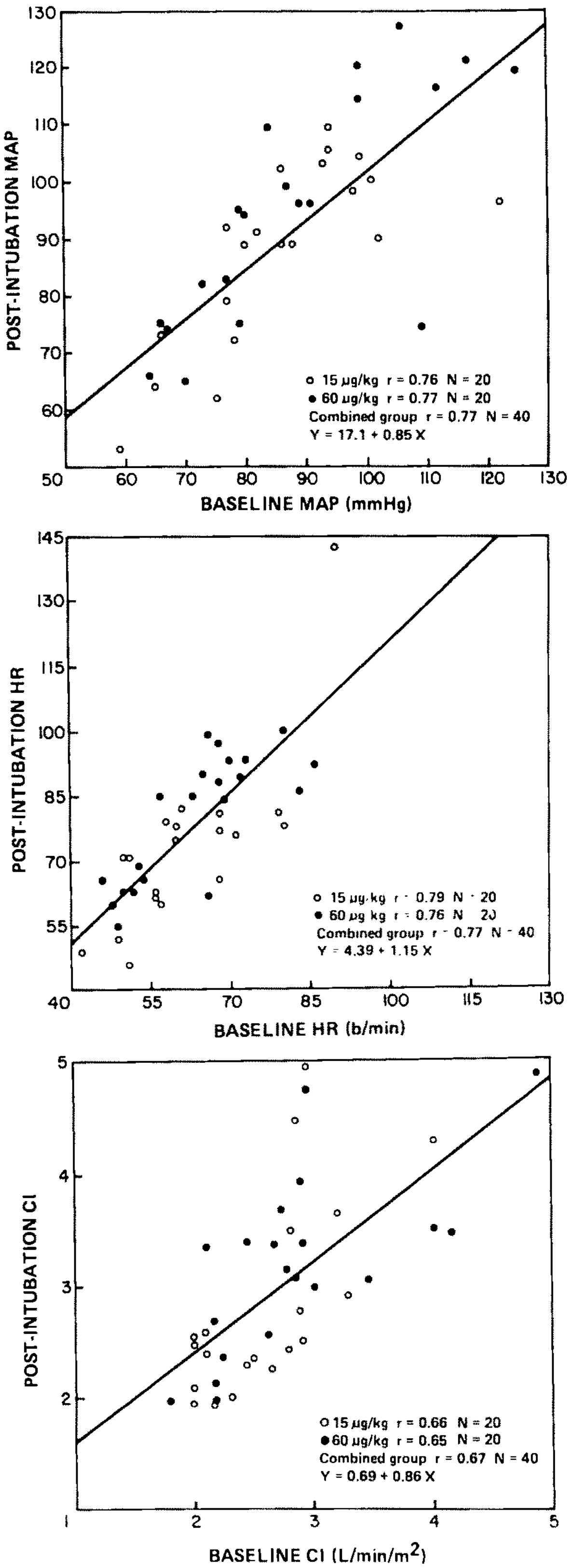

Figure 3. Heart rate, blood pressure, and cardiac index before induction and after intubation in individual patients receiving 15 or 60 μg/kg of fentanyl. Laryngoscopy and intubation were performed 3 min after the start of fentanyl administration. Postintubation values were measured 6 min after the start of drug administration.

thesia with fentanyl asserts that rapid administration of fentanyl is not associated with cortical EEG seizure activity (22). Specific studies of limited numbers of patients also showed no EEG seizure activity during fentanyl administration (23,24).

The arterial plasma fentanyl concentrations found in this study suggest that 15 μg/kg administered rapidly is near the minimum dose that will reliably produce brief anesthesia. For maintenance of anesthesia, 12–15 ng/ml (9,25) is an adequate average concentration; lower levels (8.6 ng/ml) may allow patients to become responsive to stimuli (26). Plasma fentanyl concentrations of approximately 6 ng/ml produce amnesia to visual stimuli in 50% of patients (27). Normal or nearly normal ventilatory responses to CO_2 occurs when plasma fentanyl concentrations are below approximately 1 ng/ml (28). These plasma levels are derived from various studies and pertain to patients with slowly changing fentanyl levels; application of these findings to our study is not precise, but provides estimates. In this study, the plasma concentration of fentanyl 3 min after administration of 15 μg/kg averaged 25.9 ng/ml, which is consistent with our finding of adequate anesthesia for intubation. There was no recall in our patients, but the level 13 min after induction was 4.2 ng/ml, suggesting that it would be prudent to begin administration of additional anesthetic within 10 min of induction when using 15 ng/ml fentanyl. Plasma levels at 4 hr were low enough (0.4 ng/ml) that normal ventilatory response to CO_2 would be expected (28).

Induction doses of 15 and 60 μg/kg of fentanyl had similar cardiovascular effects and were virtually identical in the correlations of postinduction cardiovascular values with baseline values. These findings were anticipated on the basis that rapid drug administration will cause high plasma levels. In rats (29), and presumably in humans, fentanyl passes rapidly from the blood into the brain. Above some minimum plasma level, fentanyl appears to have a flat dose–response curve (8), and in a small group of patients, greater doses of fentanyl produced little if any increase in the anesthetic effect above a serum concentration of 20 ng/ml (30). Our results imply that if fentanyl is administered over a short interval, an increase in effect in the dose range between 15 and 60 μg/kg of fentanyl will not occur, because the maximum acute effect in a 70-kg patient will be achieved with the first milligram of fentanyl administered. Patients with heart failure may be dependent on elevated serum catecholamine levels for homeostasis (31). In such patients, titration of fentanyl during induction may be appropriate. When titration of the cardiovascular responses to fentanyl is required, it is the first milligram that must be administered gradually to achieve a graded effect.

Because of differences in experimental methods, our results cannot be compared directly to those of Hicks et al. (13), who found that a decrease in cardiac output resulted from administration of 30 or 50 μg/kg of fentanyl. The 15-μg/kg dose in the present study produced adequate anesthesia during induction, but the 60-μg/kg dose had little or no harmful hemodynamic effect. Given the limited number of patients studied, it is not clear that doses of 15 μg/kg will be an adequate induction anesthetic for all patients with the demographic characteristics of our study group. Therefore, unless a short duration of action is important, we commonly use 30 μg/kg of fentanyl for induction of anesthesia in patients such as those included in the present study.

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Evolution of Vecuronium Requirements for Stable Mechanical Effect:

Comparison with or without Previous Succinylcholine Administration

Alain d'Hollander, MD, PhD, Sandor Agoston, MD, PhD, Luc Barvais, MD,
Jacques Massaut, MD, and Michel Baurain, MD

D'HOLLANDER A, AGOSTON S, BARVAIS L, MASSAUT J, BAURAIN M. Evolution of vecuronium requirements for stable mechanical effect: comparison with or without previous succinylcholine administration. 1985;64:319–22.

To evaluate possible interactions between residual succinylcholine and vecuronium, the amount of vecuronium required to maintain the twitch height (TH) at 10% of its initial value was measured over a 90-min period by the on-demand infusion method in two series of 15 adult patients (ASA class I–II). One group, the vecuronium treatment (V) group, received 70 $\mu g \cdot kg^{-1}$ of vecuronium and the on-demand infusion. The second group, the succinylcholine–vecuronium treatment group (SV), was given 30 $\mu g \cdot kg^{-1}$ of vecuronium and on-demand infusion 5 min after the complete recovery of TH after administration of 1 $mg \cdot kg^{-1}$ of succinylcholine. During the first 10 min, the amount of vecuronium required to maintain TH at 10% of its control was significantly greater in the group given V than in the group given SV, 15122 ± 856 (mean ± SEM) vs 9851 ± 486 $\mu g \cdot m^{-2} \cdot hr^{-1}$ ($P < 0.001$). Thereafter, the amount of vecuronium required to maintain TH at 10% of control was similar: 2808 ± 275 and 3068 ± 206 $\mu g \cdot m^{-2} \cdot hr^{-1}$. When the infusion of vecuronium was stopped after 90 min, the time required for spontaneous recovery from 25 to 75% of control TH levels was similar: 20.1 ± 3.3 min in the group given V and 18.9 ± 2.5 min in the group given SV (not significant). We conclude that after a vecuronium on-demand infusion of long duration (lasting more than 90 min), previous succinylcholine administration does not interfere with late vecuronium requirements and the spontaneous rate of recovery of TH.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium, succinylcholine.

Augmentation of neuromuscular blocking effects of different competitive neuromuscular blocking agents including vecuronium, a new monoquaternary competitive relaxant, by prior administration of succinylcholine is a well-documented phenomenon (1–3). We have recently observed augmented neuromuscular blocking effects with vecuronium for as long as 45 min after the prior administration of succinylcholine (4). The goals of the present study were twofold: first, to quantitate the amount of vecuronium needed to maintain a constant level of twitch height (TH) depression after the prior administration of succinylcholine and to compare these data to the amount of vecuronium required to maintain equal depression of TH in patients receiving vecuronium alone, as described previously (5,6); and second, to determine, once a long-duration infusion of vecuronium is stopped, whether the spontaneous rate of recovery of TH differs in patients who received prior succinylcholine administration from those receiving vecuronium alone.

Materials and Methods

Thirty (ASA class I–II) patients of both sexes, younger than 60 yr old who suffered from no neuromuscular diseases and took no drugs that could interfere with the parameters studied, were selected for the study. The study was approved by the Ethical Committee of Brussels Free University and informed consent was obtained from each patient.

Premedication consisted of oral diazepam (0.2 mg/kg), administered 60 min before induction of anesthesia. Anesthesia was induced with methohexital (1 mg/kg). When the patient was unconscious, a displacement transducer (7) was used to record the me-

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Address correspondence to Dr. d'Hollander, Service d'Anesthésie, Hôpital Brugmann, place Van Gehuchten, 4 - B-1020 Bruxelles, Belgium.

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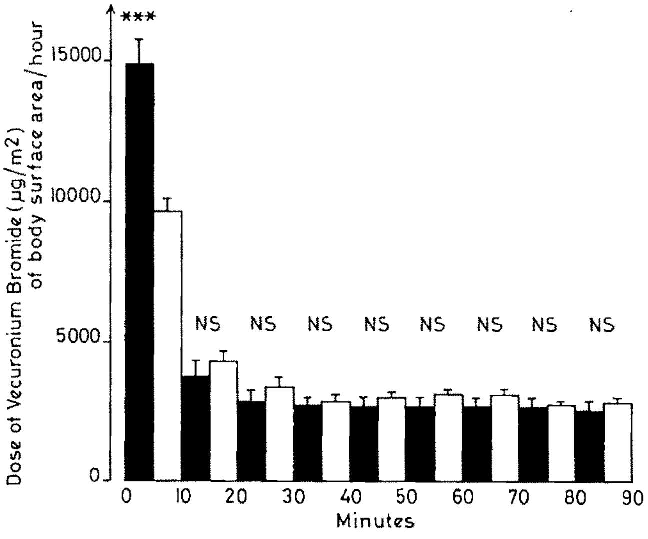

Figure 1. Evolution of the cumulated requirements (loading doses and on-demand infusion) in group V (■) and in group SV (□). Mean ± SEM. ***, $P < 0.001$; NS, not significant, two tailed unpaired t-test.

chanical activity of the adductor pollicis stimulated electrically (rectangular wave, 0.2-msec duration, supramaximal at a frequency of 0.1 Hz) via the cubital nerve at the level of the wrist. Ventilation was ensured manually with a circle circuit containing 50% nitrous oxide in oxygen until tracheal intubation was performed at the moment of maximal TH depression. Analgesia was maintained thereafter by repeated injections of fentanyl, and ventilation was controlled mechanically with a semiclosed circuit containing O_2/N_2O 1:2 vol/vol L and regulated to maintain end-tidal CO_2 at 5 ± 0.1% (HP CO_2 analyzer) or arterial P_{CO_2} between 36 and 42 mm Hg.

The patients were distributed in a random manner into two groups of 15. In the group given V, patients received only vecuronium as described previously (7): a loading dose of 70 µg/kg immediately followed by an on-demand perfusion regulated to maintain TH at 10% of its control value. In the group given SV, patients received succinylcholine (1 mg/kg) followed by vecuronium starting 5 min after the complete recovery of TH. In these patients, the vecuronium was administered using a loading dose of 30 µg/kg followed by an on-demand infusion adjusted to maintain the mechanical activity of the adductor pollicis at 10% of its initial value. The different loading doses chosen for the two groups were selected on the basis of our previous studies showing that during fentanyl–N_2O anesthesia, a loading dose of 70 µg/kg of vecuronium reduced TH value to 5–10% of its initial value (7); whereas after succinylcholine, 40 µg/kg of vecuronium depressed the TH to about 4% of control (4). In both groups, the perfusion of vecuronium was maintained for at least 90 min and then was either stopped or continued if surgical requirements necessitated continual relaxation.

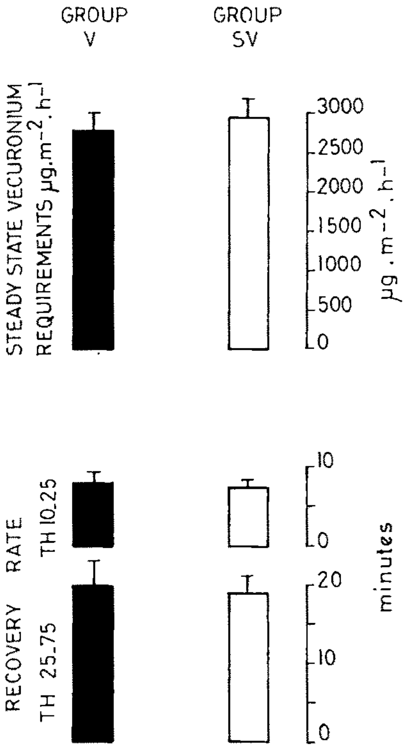

Figure 2. Mean steady-state vecuronium requirements (noted between 30 and the 90 min), TH10-25, and TH25-75 recovery rates observed in the V and SV series (15 patients in each group). These values were not significantly different.

The following parameters were studied: first, the amount of vecuronium ($\mu g{\cdot}m^{-2}{\cdot}hr^{-1}$) injected in loading doses, and/or infused on-demand, recorded at 10-min intervals after administration of the relaxant; second, the time required for recovery of TH from 10 to 25% of control after termination of the vecuronium infusion; and third, the time required for recovery of TH from 25 to 75% of control after termination of the infusion of vecuronium.

Paired (within groups) and unpaired (between groups) comparisons using two-tailed Student's t-tests were employed for evaluation of statistical significance using methods described in the SPSS programs (8).

Results

Ages, weights, and heights of the patients in both groups were similar (mean ± SEM): 40 ± 2.4 and 40 ± 3.9 yr; 59.8 ± 8.6 and 69.3 ± 3.3 kg; and 172 ± 4 and 167 ± 4 cm in the groups given V and SV, re-

Table 1. Evolution of Vecuronium Requirements ($\mu g \cdot m^{-2} \cdot hr^{-1}$) Determined with the On-Demand Infusion Method in the Group Given V (Vecuronium Alone) and the Group Given SV (Succinylcholine followed by Vecuronium)

	0–10 min	10–20 min	20–30 min	30–40 min	40–50 min	50–60 min	60–70 min	70–80 min	80–90 min
Group V	15127	3868	3044	2827	2874	2826	2821	2792	2664
(n = 15)	± 856[a]	± 560[b,c]	± 422[c]	± 258[c]	± 331[c]	± 306[c]	± 273[c]	± 269[c]	± 286[c]
Group SV	9851	4337	3546	3055	3152	3242	3191	2829	2942
(n = 15)	± 486	± 381[b,c]	± 418[c]	± 241[c]	± 199[c]	± 250[c]	± 268[c]	± 224[c]	± 266[c]

[a] Mean ± SEM.
[b] Two tailed paired t-test within a group (period 0–10 min taken as reference).
[c] $P < 0.001$.

spectively. In the group given SV, the maximal paralysis obtained after 1 mg/kg of succinylcholine was 0.9 ± 2.5% of control TH (range, 0–10%). Complete and stable recovery of the TH was seen after 13 ± 2 min. The evolution of vecuronium requirements within the groups given V and SV are shown in Figure 1 and in Table 1. Vecuronium requirements were significantly different only during the first 10 min. Mean steady-state vecuronium requirements between 30 and 90 min were similar: 2808 ± 275 and 3068 ± 206 $\mu g \cdot m^{-2} \cdot hr^{-1}$ in the groups given S and SV, respectively.

The time in minutes from the end of the perfusion of vecuronium to the point where the TH reached 25% of its initial value (TH 10–25 period) averaged 8.8 ± 0.9 in group V and 7.7 ± 1.1 for the group given SV (not significant). The TH 25–75 period averaged 20.1 ± 3.3 min in the group given V and 18.9 ± 2.5 min in the group given SV (not significant) (see Fig. 2).

Discussion

Previous reports have demonstrated that the neuromuscular blocking effects of vecuronium are augmented by the prior injection of succinylcholine (2,3). In these reports, the interval between the administration of the two relaxants was about 20 min. More recently, we have observed that, even by increasing this interval to 45 min, vecuronium neuromuscular effects remained augmented and that the rate of spontaneous recovery of TH from the effect of vecuronium was decreased by prior administration of succinylcholine (4). The present study was undertaken first to observe the effect of prior succinylcholine administration upon the evolution of the vecuronium requirements during prolonged (more than 90 min) on-demand infusions of vecuronium, and second to determine whether the rate of spontaneous recovery of TH rate remained prolonged when the interval between bolus administration of succinylcholine and the end of the vecuronium infusion exceeded 90 min, as it does when the interval between succinylcholine and vecuronium administration is less than or equal to 45 min. The present results confirm the augmented paralyzing action of vecuronium by prior succinylcholine administration because the quantity of vecuronium necessary to lower the TH to 10% of its initial value was markedly reduced in the patients in the group given SV compared with those of the group given V during the first 10 min of infusion.

As a consequence of different loading doses in both groups, a prefixed level of paralysis can be expected to be obtained with a lower vecuronium plasma concentration in the SV-treated patients compared with patients receiving vecuronium alone (V group). Thereafter, the difference between the vecuronium plasma concentration in both groups will become progressively less because the vecuronium requirements in the SV-treated patients remained constantly slightly higher than the requirements noted in the subjects of the group given V (see Fig. 1). During the last 60 min before the cessation of vecuronium infusion, the vecuronium requirements of both groups were not significantly different. One may, therefore, conclude that the plasma clearance remained similar in the patients of the two groups studied. This indicates that plasma vecuronium clearance has not been markedly altered by previous succinylcholine administration. In these conditions, it is not a surprise to observe similar spontaneous vecuronium TH recovery rates in the groups given V and SV because the disappearance of paralysis produced by nondepolarizing muscle relaxants is, to a great extent, related to the plasma clearance of the drug at the moment the TH begins to recover (9,10).

In conclusion, in case of on-demand vecuronium infusion of long duration (≥90 min), previous administration of succinylcholine does not interfere with the TH recovery rates once the vecuronium infusion is stopped. The present results suggest that the action of 1 mg/kg of succinylcholine upon the dose–effect relationships of vecuronium, established by on-demand infusion, has totally disappeared after infusions lasting more than 90 min.

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Large Volume Crystalloid Resuscitation Does Not Increase Extravascular Lung Water

T. James Gallagher, MD, Michael J. Banner, RRT, and Peggy A. Barnes, MD

GALLAGHER TJ, BANNER MJ, BARNES PA. Large volume crystalloid resuscitation does not increase extravascular lung water. Anesth Analg 1985;64:323–6.

The purpose of this study was to determine whether Ringer's lactate solution increases extravascular lung water (EVLW) during resuscitation after hemorrhagic shock. Ten sheep anesthetized with thiamylal were bled to a mean arterial pressure (MAP) of 50 mm Hg; further bleeding maintained that pressure for 30 min. Resuscitation fluid consisted of Ringer's lactate solution in volumes necessary to restore and maintain for 1 hr MAP, pulmonary capillary wedge pressure (PCWP), and cardiac index at levels equal to those measured before bleeding. After volume replacement, the colloid oncotic pressure (COP) − PCWP gradient (COP − PCWP) decreased from 12 ± 3 to 2 ± 5 mm Hg ($P < 0.001$). After volume restoration, COP decreased from 19 ± 8 mm Hg to 12 ± 2 mm Hg ($P < 0.001$). Despite the large volume of fluid administered, EVLW did not increase. Crystalloid resuscitation does not necessarily increase EVLW despite significant decreases in COP and COP − PCWP gradient.

Key Words: SHOCK—hemorrhagic. LUNG—water content.

Balanced electrolyte-containing solutions can reliably effect adequate fluid resuscitation in the hypovolemic patient. The large volumes usually required and the lack of protein in the solution can, however, significantly reduce colloid oncotic pressure (COP). Because COP predominates as the major Starling factor to maintain fluids in the intravascular compartment, large volumes of crystalloid, which decrease COP, may increase interstitial water, particularly in the lung. The purpose of this study was to determine if, after hemorrhagic shock, fluid resuscitation with crystalloid (Ringer's lactate solution) would increase extravascular lung water.

Materials and Methods

Ten sheep weighing between 25 and 50 kg were initially anesthetized with thiamylal sodium (15 mg/kg). Anesthesia was then maintained by a continuous infusion of the same agent mixed with Ringer's lactate solution. After tracheal intubation, mechanical ventilation was maintained with a tidal volume of 15 ml/kg and a frequency of 8–10 breaths/min to keep Pa_{CO_2} between 35 and 45 mm Hg. End-expiratory pressure was 0 cm H_2O throughout the study. $F_{I_{O_2}}$ remained constant at 0.5.

A 7-fr, balloon-tipped, flow-directed pulmonary artery catheter was inserted percutaneously in the internal jugular vein to determine pulmonary capillary wedge pressure (PCWP) and thermodilution cardiac index (CI). A 5-fr, thermistor-tipped catheter was placed via the carotid artery into the distal aorta to measure systemic arterial blood pressure, mean arterial pressure (MAP), and extravascular lung water (EVLW). EVLW was measured with the thermal dye technique described by Lewis and Elings (1).

Arterial and mixed venous blood samples were obtained anaerobically for direct measurement of oxygen saturation (Instrumentation Labs 282) and blood-gas tensions (Instrumentation Labs 813); venous admixture (*Qsp/Qt*) was calculated by standard formula. COP was also measured directly with an oncometer (Wescor). The COP − PCWP gradient was computed by simple subtraction.

After baseline measurements, each animal was bled via a heparinized peripheral arterial catheter to a MAP of 50 mm Hg, which was maintained for 30 min by subsequent bleeding as necessary. Measurements were repeated at the end of that 30-min interval. Then resuscitation with Ringer's lactate solution com-

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Address correspondence to Dr. Gallagher, Department of Anesthesiology, Box J-254, J. Hillis Miller Health Center, Gainesville, FL 32610.

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Table 1. Effects of Shock and Fluid Resuscitation[a]

			Fluid resuscitation	
	Baseline	During shock	Initial	After 1 hr
Mean arterial pressure (mm Hg)	106 ± 9	50 ± 0[b]	89 ± 17[b]	108 ± 26
Pulmonary capillary wedge pressure (mm Hg)	7 ± 3	5 ± 3[b]	9 ± 3	10 ± 5[b]
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.5 ± 0.3	1.4 ± 0.5[b]	2.7 ± 0.6	3.6 ± 0.7
Stroke volume (ml)	22 ± 7	12 ± 4[b]	22 ± 6	30 ± 14[b]
Ringer's lactate solution (ml)	68 ± 13	—	493 ± 209[b]	1215 ± 686[b]
Colloid oncotic pressure (COP) (mm Hg)	19 ± 0.8	18 ± 0.8	13 ± 1.0[b]	12 ± 2.0[b]
COP − pulmonary capillary wedge pressure (mm Hg)	12 ± 3	13 ± 4	3 ± 3[b]	2 ± 5[b]
Extravascular lung water (ml)	382 ± 208	373 ± 191	342 ± 128	339 ± 137
PaO_2 (mm Hg)	200 ± 43	215 ± 47	206 ± 48	174 ± 61
Venous admixture (%)	2 ± 1.8	1 ± 1.3	2 ± 1.6	5 ± 5[b]

[a] Values are means ± SD.
[b] $P < 0.05$ compared with baseline.

menced and was continued until baseline values for CI, MAP, and PCWP were restored. The infusion was then continued for 1 hr at rates sufficient to maintain baseline values. The values after 1 hr of infusion were compared with baseline values and those just before the initiation of fluid resuscitation. Results are given as means ± SD. Statistical analysis included paired *t*-test analysis and analysis of variance. Statistical significance was assumed with P values less than 0.05.

Results

Blood loss averaged 320 ± 185 ml. After the initial fluid resuscitation, CI and PCWP returned to baseline levels. However, further fluid administration was required to restore MAP to its baseline value (Table 1). Resuscitation was associated with significant decreases in COP and COP − PCWP (Fig. 1). Despite these changes, EVLW and blood-gas values remained constant throughout the study (Table 1, Fig. 2). The initial amount of Ringer's lactate solution infused during resuscitation averaged 493 ± 209 ml; the final amount after 1 hr averaged 1215 ± 686 ml.

Discussion

The thermal dye technique used in this study to measure EVLW has been evaluated extensively in both humans and animals, and in-vivo, indirect measurements of the ratio between wet and dry lung tissue made just before death have shown a significant correlation with wet-to-dry ratios determined at autopsy (correlation coefficient, $r = 0.96$) (1). Although there may be some question of the accuracy of individual values, the results of controlled studies using statistically valid numbers of observations are reproducible, and changes in either direction can be clearly documented.

The model used in this study may not entirely reflect changes associated with trauma and shock in humans. Trauma, when associated with shock, may, for example, stimulate release of various vasoactive substances that can alter capillary membrane integrity and ultimately the amount of EVLW. However, experimental hemorrhagic shock by itself has not been associated with any alteration of capillary integrity (2).

In this study, large volumes of fluid (1000 ml/50 kg) were needed to restore MAP to original levels. Because CI and PCWP were identical before and after fluid resuscitation, we can infer that no myocardial damage occurred; maintenance of stroke volume reinforces this inference.

With crystalloid resuscitation, most of the fluid does not remain in the intravascular compartment. Most authorities feel that within 1 hr, as much as 80% may relocate into the interstitial compartment (Moss J, personal communication). This helps explain the large volumes necessary after significant blood loss. In the present study, sufficient crystalloid remained in the intravascular compartment to significantly decrease both COP and the COP − PCWP gradient. However, EVLW remained unaffected. While by the end of the study, Qsp/Qt significantly increased, a change from 2 to 5% has little if any clinical relevance.

The stability of EVLW despite the voluminous crystalloid resuscitation has several possible explanations. Starling's equation mathematically describes fluid dynamics within the alveolar capillary membrane:

$$\dot{Q} = K_{F,C}\,[(P_C - P_T) - \delta_C\,(\pi_C - \pi_T)]$$

where $\dot{Q}$ is the filtration rate across capillary membrane, $K_{F,C}$ the filtration coefficient, P_C the capillary hydrostatic pressure, P_T the interstitial hydrostatic pressure, π_C the capillary oncotic pressure, π_T the interstitial oncotic pressure, and δ_C the reflection coefficient (3).

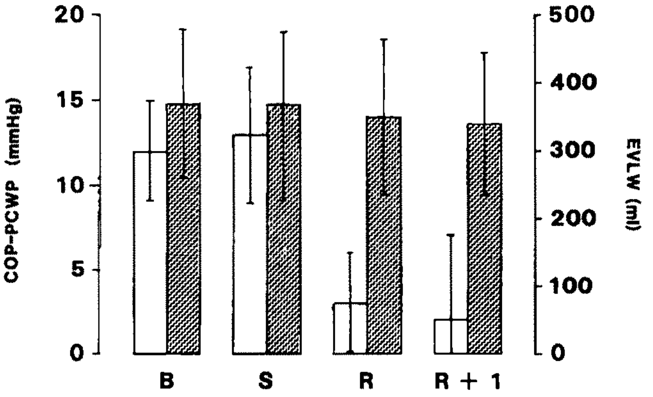

Figure 1. Colloid oncotic pressure minus pulmonary capillary wedge pressure gradient (open bars) vs extravascular lung water (hatched bars) during baseline measurements (B), during shock (S), during resuscitation (R), and after 1 hr of resuscitation (R + 1).

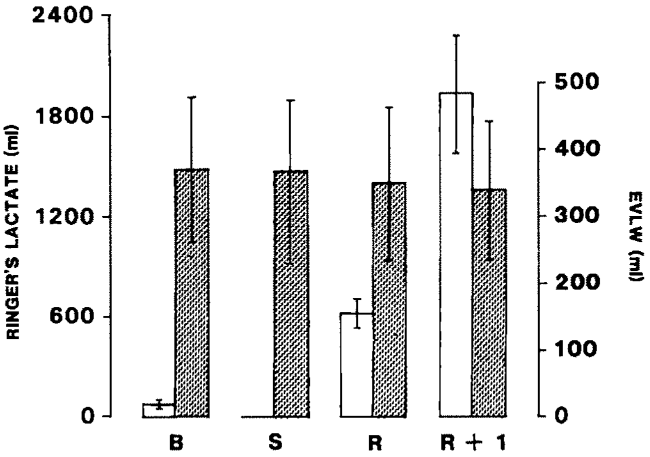

Figure 2. Volume of Ringer's lactate solution administered (open bars) vs extravascular lung water (hatched bars) during baseline measurements (B), during shock (S), during resuscitation (R), and after 1 hr of resuscitation (R + 1).

Most of the Starling forces are difficult to measure clinically. We assume that pulmonary microvascular pressure represents PCWP plus 40% of the difference between pulmonary artery and wedge pressures (4). We currently have no easy or reliable method to evaluate clinically or experimentally interstitial hydrostatic or oncotic pressure. Attempts to catheterize the interstitial space for those determinations significantly distort the pulmonary interstitial anatomy and, thus, conceivably can affect the measurements (5). Capillary permeability at best can only be calculated from the other variables.

Although hemorrhagic shock may affect sodium deposition along the alveolar–capillary interface (2), there is minimal evidence of any increase in pulmonary capillary permeability during hemorrhagic shock. More often altered permeability develops during sepsis as a result of the direct action of toxins at the alveolar–capillary interface (6).

During the brief period of this study, the filtration coefficient ($K_{F,C}$) should have remained constant. Conceivably, if interstitial fluid were to expand the interstitial space, the disruption of the pulmonary architecture could increase the area of interface for fluid exchange (7). Even greater fluid flux might occur and, thus, possibly further increase fluid in the lung; however, we did not detect any such increase.

Because we can accurately measure only COP clinically, any evaluation of pulmonary interstitial fluid flux or accumulation is speculative (8). Having accurate data for only one of five variables thus makes prediction of lung water changes difficult. For example, if COP were to decrease, any resultant increase in fluid flux into the pulmonary interstitial space could increase interstitial hydrostatic pressure. In turn, the increase in interstitial pressure would oppose any further fluid movement into the interstitium (9). Only if no other variables changed would COP or COP − PCWP accurately predict fluid flux into pulmonary interstitial space. However, because volume and compliance are limited, even a small fluid shift could affect serum and oncotic and hydrostatic pressures in the interstitium. Furthermore, an increase in pulmonary interstitial fluid may still not affect EVLW because pulmonary lymphatic drainage may also increase to maintain a normal EVLW (10). Only after such a compensatory mechanism has been overwhelmed might fluid actually begin to accumulate in the lung interstitium.

In conclusion, large volume crystalloid resuscitation in an ovine model of hemorrhagic shock does not increase pulmonary EVLW. Furthermore, in this model, a large decrease in COP or in the COP − PCWP gradient poorly predicted increases in interstitial fluid.

The authors thank Lynn M. Carroll for editorial assistance.

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ANESTH ANALG
1985;64:327–34

Cardiovascular Effects of Esmolol in Anesthetized Humans

Paul G. Menkhaus, MD, J.G. Reves, MD, Igor Kissin, MD, PhD, J. Michael Alvis, MS, Ann V. Govier, MD, Paul N. Samuelson, MD, William A. Lell, MD, C.E. Henling, MD, and Edwin Bradley, PhD

MENKHAUS PG, REVES JG, KISSIN I, ALVIS JM, GOVIER AV, SAMUELSON PN, LELL WA, HENLING CE, BRADLEY E. Cardiovascular effects of esmolol in anesthetized humans. Anesth Analg 1985;64:327–34.

We studied the cardiovascular effects of esmolol, a newly synthesized β-adrenocepter antagonist, in anesthetized humans. Forty patients (four groups of 10 each) with ischemic heart disease and normal ventricular function were anesthetized with diazepam, pancuronium, and N_2O in O_2. Esmolol was given by continuous infusion in cumulative doses of 1100 μg/kg (group 1), 2000 μg/kg (group 2), and 2700 μg/kg (group 3); a control group received no esmolol. Infusion of esmolol was begun 3 min prior to and ended 4 min after tracheal intubation. All three doses of esmolol significantly ($P < 0.001$) attenuated the heart rate responses to intubation. Rate–pressure products were significantly ($P < 0.001$) lower in esmolol-treated patients than in controls after intubation, but ST-segment changes compatible with ischemia occurred in one patient in each group. Increases in heart rate were associated with significant increases in plasma norepinephrine levels ($r = 0.45$, $P = 0.02$) in the control group, but not in esmolol-treated patients, a demonstration that esmolol antagonizes the β-adrenergic effects of norepinephrine. The effect of esmolol on heart rate was absent 5 min after cessation of infusion, and plasma levels of esmolol were undetectable in 26 of 30 treated patients 15 min after the termination of esmolol infusion. Esmolol has a rapid onset and short duration of effect. It can be used safely during anesthesia in patients with normal ventricular function to attenuate cardiac response to sympathetic stimulation.

Key Words: SYMPATHETIC NERVOUS SYSTEM—β-ADRENERGIC ANTAGONISTS, esmolol. HEART—MYOCARDIAL FUNCTION, β-adrenergic blockade.

Esmolol (methyl 3-(4-(2-hydroxy-3-(isopropylamino) propoxy) phenyl) proprionate hydrochloride) is a water-soluble β-adrenoceptor antagonist with rapid onset and ultrashort duration of action (1,2). Potentially, it is an excellent drug to prevent or treat undesirable increases in heart rate (HR) and contractility that may occur during general anesthesia and surgery in response to increased sympathetic activity. These increases are likely to occur in response to such stimuli as laryngoscopy, tracheal intubation, skin incision, and surgical manipulation. Probably best documented are increased adrenergic activity (3,4) and resultant increases in heart rate and blood pressure (5,6) in response to tracheal intubation. Increases in heart rate may be associated with ST-segment changes that indicate myocardial ischemia in patients with coronary artery disease (7). β-Adrenoceptor blockade minimizes increases in heart rate and myocardial contractility (primary determinants of oxygen consumption) by attenuating the positive chronotropic and inotropic effects of increased adrenergic activity. This is particularly desirable in patients with ischemic heart disease.

The present investigation was designed to examine the cardiovascular pharmacology of esmolol during general anesthesia. The investigation was designed to determine the dosage of esmolol that is safe and effective in reducing cardiovascular responses to laryngoscopy and tracheal intubation in anesthetized humans.

Methods

Institutionally approved informed consent was obtained in 40 patients scheduled for elective myocardial revascularization surgery. Patients were excluded for reasons listed in Table 1. The patients were divided into four groups: one untreated group (control) and three groups (experimental) given different dosages of esmolol infusion (see below). Patients were not

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Address correspondence to Dr. Reves, Department of Anesthesiology, Duke University, Durham, NC 27710.

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Table 1. Exclusion Criteria

- Pregnancy
- History of atrial flutter/fibrillation
- A-V conduction block greater than first degree
- Myocardial infarction within 4 weeks prior to study
- Systolic blood pressure less than 100 mm Hg
- Diastolic blood pressure less than 50 mm Hg
- History of congestive heart failure
- Chronic obstructive pulmonary disease, bronchial asthma, or history of bronchospasm
- Clinical or laboratory evidence of severe renal, hepatic, or neurological disease
- History of drug allergy to β-adrenergic blocking drugs
- Concurrent drug therapy with:
  - β-Adrenergic blockers other than propranolol
  - β-Adrenergic stimulants
  - α-Adrenergic blockers
  - α-Adrenergic stimulants
  - Antiarrhythmics
  - Digoxin/digitoxin
  - Adrenergic augmenting psychotropic drugs
  - Reserpine or guanethidine

randomly assigned as it was felt that lower dosages should be administered before higher dosages in this initial use of esmolol in anesthetized humans. Demographic data as well as the type and dosage of chronic medications are shown in Table 2. Patients receiving propranolol, calcium channel blockers, or both received their last dose no later than 16 hr before induction of anesthesia. Preoperative nitrate therapy was continued until the time of surgery.

Premedication consisted of oral diazepam, 0.15 mg/kg, morphine sulfate, 0.1 mg/kg intramuscularly, and scopolamine, 0.3 to 0.4 mg intramuscularly, 60–90 min before induction of anesthesia. Upon arrival in the operating suite patients were monitored with an ECG, either Lead II or V_5, and a 16-gauge intravenous catheter was inserted in an upper extremity vein. Also, an 18-gauge radial arterial catheter was placed with the patient under local anesthesia. In five patients in each group, an 8F (#496124, Argon Medical Corp) introducer was placed into the right internal jugular vein and a 7F balloon flotation thermodilution pulmonary arterial catheter (model 93A-303-7F, American Edwards Lab) was floated into the pulmonary artery. Ringer's lactate solution was administered at this time to bring the pulmonary artery occlusion pressure (PAOP) to 10 mm Hg or a value equal to the PAOP at the time of preoperative cardiac catheterization, whichever was lower.

Direct measurements during the study included: ECG; HR; systolic and diastolic systemic, pulmonary arterial, and central venous pressures; and mean pulmonary artery occlusion pressures (Hewlett-Packard oscilloscope 78304A, ECG amplifier module 78203C with transducer module 78205C, preamplifier module 8802A, interface 8826A, and recorder 7758A; and Gould Statham P23 ID pressure transducers); cardiac output, measured by thermodilution (Gould Statham SP1425 and recorder SP2010); and end-tidal CO_2, maintained between 35 and 45 mm Hg. Cardiac output measurements were averaged from two determinations. Derived values consisted of mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), rate–pressure product (RPP), stroke volume index (SVI), and left ventricular stroke work index (LVSWI). Plasma norepinephrine (NE) concentrations were measured by a modification of the high pressure liquid chromatography (HPLC) method of Keller et al. (8). Plasma esmolol levels were determined by an HPLC method using an ultraviolet detection system at 229 nm. (All plasma blood levels were performed in the analytical drug laboratories of American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085.)

After placement of the monitoring devices, patients rested for 10 min before induction of anesthesia. Baseline hemodynamic values were recorded 1 min before induction. Anesthesia was induced with diazepam, 0.5 mg/kg, and pancuronium, 0.1 mg/kg, given intravenously over 20 sec while the patient was breathing 50% N_2O in O_2. Esmolol infusion was started 3 min after induction. All patients in the treatment groups received esmolol 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the first minute. Thereafter, esmolol infusion varied: group 1 received 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional 6 min; group 2 received 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional minute followed by 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min; group 3 received 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional 2 min followed by 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 min. Laryngoscopy occurred 6 min after induction (i.e., 3 min after beginning esmolol infusion) in all groups. Hemodynamic measurements were made at baseline and 3, 6, 7, 9, 10, 15, and 25 min after induction of anesthesia. Cardiac output and plasma NE levels were measured at baseline and 3, 6, 9, and 25 min after induction of anesthesia. Blood samples for subsequent measurements of plasma levels of esmolol were drawn at 6, 9, and 25 min after induction of anesthesia. The study scheme and stages are illustrated in Figure 1.

All continuously varying measurements were summarized as the mean ± SD and SEM. The results for variables measured over time were initially tested for the effects of time and the differences between groups using a repeated measures analysis of variance. Interest focused on comparisons between groups at each

Table 2. Comparative Patient Values[a]

	Control (n = 10)	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)
Age (yr)	57.1 ± 2.5	54.9 ± 3.2	52.8 ± 2.6	58.9 ± 1.7
Weight (kg)	78.7 ± 3.6	81.9 ± 4.6	87.9 ± 4.0	81.0 ± 3.3
Height (cm)	174.7 ± 1.6	173.7 ± 2.0	175.7 ± 3.5	174.6 ± 2.1
BSA (m^2)	1.97 ± 0.05	2.02 ± 0.06	2.09 ± 0.06	1.99 ± 0.05
Gender				
Male	10	8	10	10
Female	0	2	0	0
Preoperative SBP (mm Hg)	133.5 ± 4.8	123.6 ± 3.4	123.9 ± 3.3	125.7 ± 3.7
Preoperative DBP (mm Hg)	77.8 ± 3.2	74.5 ± 3.1	75.7 ± 2.4	73.1 ± 2.2
Preoperative HR (beats/min)	75.1 ± 2.9	69.6 ± 3.2	72.9 ± 3.7	75.9 ± 4.1
Hypertension history (requiring therapy)	0	2	2	0
Types and dosage of chronic antianginal therapy[a]				
Propranolol				
Number of patients	4	6	7	5
Daily dose (mg)	65 ± 19.2	166 ± 46.6	111 ± 13.9	112 ± 17.5
Calcium channel blockers				
Number of patients	6	9	9	8
Nitroglycerin (topical)				
Number of patients	6	5	3	6
Daily dose (mg)	13.7 ± 7.8	50 ± 19.2	21 ± 13.5	17 ± 11.5
Isosorbide dinitrate				
Number of patients	4	3	1	3
Daily dose (mg)	50 ± 16.3	53 ± 14.4	80 ± 0	67 ± 10.9

[a] Mean values ± SEM. Abbreviations: BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

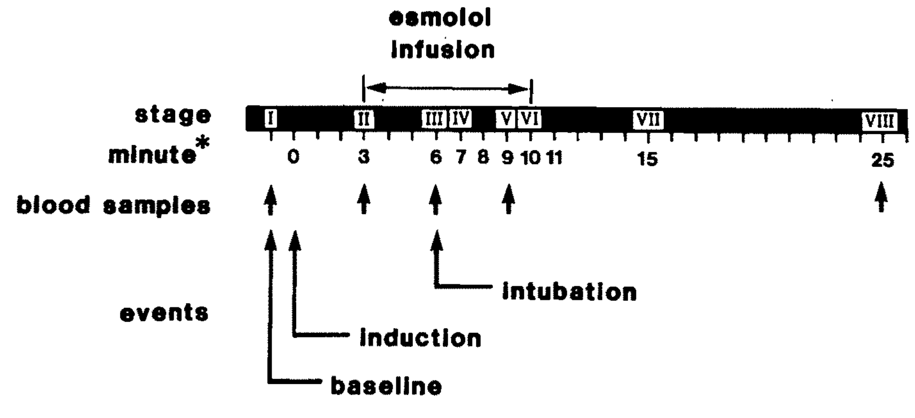

Figure 1. Infusion of esmolol at stages I–VIII in clinical study. *Hemodynamic measurements taken at the numbered minutes.

time and between times for each group. Between-group comparisons were performed by a one-factor analysis of variance computed at each time. Between-time comparisons used a randomized complete block analysis for each group. When the analysis of variance F-test was significant, pairwise comparisons between group means or between different time means were performed by Fisher's protected least significant difference test (9). All attributes and characteristics were summarized as counts and percents. Comparisons of attributes between groups used the χ^2 statistic for contingency tables. Differences were considered statistically significant if $P < 0.05$. All computations were performed with the aid of the Statistical Analysis System (10).

Results

Patients in the four groups had similar demographic data (age, sex, weight, height, body surface area, preoperative blood pressure and heart rate, and history of hypertension requiring therapy) (Table 2). There was also no significant difference between the groups in the numbers of patients receiving chronic antian-

Table 3. Hemodynamic Values

Event	HR	SBP	DBP	MAP	CI	PCWP	SPAP	PAD	MPAP
Control	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 5)	(n = 5)	(n = 5)	(n = 5)
Stage I	71 ± 4.3	152 ± 8.1	73 ± 1.9	100 ± 3.7	2.53 ± 0.15	11 ± 2.9	28 ± 3.7	13 ± 3.5	18 ± 3.5
Stage II	82 ± 4.3	146 ± 9.4	75 ± 2.5	98 ± 4.6	2.64 ± 0.23	14 ± 2.0	28 ± 4.3	14 ± 2.0	18 ± 2.1
Stage III	84 ± 3.3	145 ± 9.1	74 ± 3.1	98 ± 4.9	2.57 ± 0.13	9 ± 1.4	27 ± 2.6	13 ± 1.8	18 ± 2.0
Stage IV	102 ± 3.9	191 ± 8.4	104 ± 4.8	133 ± 5.6					
Stage V	98 ± 3.4	181 ± 11.0	97 ± 6.4	125 ± 7.6	2.83 ± 0.08	8 ± 2.6	25 ± 2.8	13 ± 2.7	16 ± 2.7
Stage VI	96 ± 4.3	162 ± 8.9	84 ± 3.4	110 ± 4.8					
Stage VII	86 ± 7.4	144 ± 6.8	78 ± 4.7	100 ± 5.2					
Stage VIII	77 ± 4.8	115 ± 3.6	65 ± 3.2	82 ± 3.4	2.07 ± 0.07	6 ± 1.8	20 ± 2.1	10 ± 2.1	13 ± 2.1
Group 1	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 5)	(n = 5)	(n = 5)	(n = 5)	(n = 5)
Stage I	69 ± 2.8	142 ± 6.5	66 ± 2.1^{d}	91 ± 3.3	2.43 ± 0.09	9 ± 0.8	27 ± 1.6	13 ± 0.8	18 ± 0.8
Stage II	82 ± 4.6	127 ± 7.1	70 ± 4.1	89 ± 4.6	2.43 ± 0.23	8 ± 1.9	24 ± 2.5	13 ± 1.7	16 ± 1.9
Stage III	76 ± 3.2	120 ± 8.2	62 ± 3.9	82 ± 4.9^{d}	2.13 ± 0.23^{d}	8 ± 1.9	23 ± 3.1	12 ± 2.0	15 ± 2.3
Stage IV	86 ± 3.8^{f}	168 ± 8.9	92 ± 6.5	117 ± 7.0					
Stage V	86 ± 3.7^{e}	162 ± 8.2	83 ± 4.7	110 ± 5.1	2.73 ± 0.33	9 ± 1.9	32 ± 2.5	17 ± 1.9	22 ± 2.1
Stage VI	83 ± 3.1^{e}	156 ± 7.9	86 ± 3.0	109 ± 3.8					
Stage VII	82 ± 2.6	140 ± 4.7	24 ± 3.6	96 ± 3.1					
Stage VIII	75 ± 2.2	128 ± 4.9	68 ± 3.4	91 ± 3.5	2.51 ± 0.09^{d}	8 ± 2.3	19 ± 2.2	9 ± 1.8	15 ± 1.0
Group 2	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 5)	(n = 5)	(n = 5)	(n = 5)	(n = 5)
Stage I	70 ± 4.0	145 ± 6.6	66 ± 3.4^{d}	92 ± 3.6	2.55 ± 0.18	9 ± 1.5	29 ± 4.4	14 ± 3.6	19 ± 3.8
Stage II	81 ± 5.3	129 ± 5.6	65 ± 3.6	87 ± 3.6	2.51 ± 0.09	15 ± 6.3	26 ± 4.9	14 ± 4.8	18 ± 4.8
Stage III	75 ± 3.6	109 ± 4.9	56 ± 3.7	74 ± 3.8^{f}	2.33 ± 0.08	9 ± 0.9	27 ± 6.0	14 ± 4.0	18 ± 4.3
Stage IV	85 ± 2.5^{f}	155 ± 8.7^{f}	86 ± 5.8^{d}	109 ± 6.5^{e}					
Stage V	82 ± 2.4^{f}	147 ± 8.6^{e}	78 ± 5.1^{d}	101 ± 5.7^{e}	2.55 ± 0.12	14 ± 3.7	32 ± 6.3	19 ± 5.4	23 ± 5.7
Stage VI	82 ± 2.3^{e}	135 ± 8.2	70 ± 4.0	92 ± 5.1^{a,d}					
Stage VII	82 ± 3.3	129 ± 4.0	68 ± 3.3	89 ± 3.0					
Stage VIII	75 ± 5.1	118 ± 5.5	63 ± 4.3	93 ± 3.9^{b,d}	2.07 ± 0.10^{a}	9 ± 1.7	23 ± 2.0	11 ± 1.2	17 ± 2.3
Group 3	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 4)	(n = 4)	(n = 4)	(n = 4)	(n = 4)
Stage I	68 ± 4.0	130 ± 5.7^{d}	64 ± 2.7^{d}	86 ± 3.4^{e}	2.13 ± 0.15	11 ± 2.2	24 ± 3.7	13 ± 2.8	16 ± 3.1
Stage II	78 ± 3.6	122 ± 7.7^{d}	67 ± 4.0	85 ± 5.1^{d}	2.60 ± 0.12	10 ± 3.0	22 ± 4.0	12 ± 3.1	15 ± 3.3
Stage III	72 ± 2.6^{e}	105 ± 5.7^{d}	57 ± 4.1^{d}	73 ± 4.5^{f}	2.47 ± 0.10	9 ± 2.7	22 ± 4.6	11 ± 2.1	14 ± 2.7
Stage IV	83 ± 1.9^{f}	151 ± 8.5^{f}	88 ± 5.3	109 ± 6.2^{e}					
Stage V	81 ± 2.1^{f}	142 ± 8.6^{f}	79 ± 5.1^{d}	100 ± 6.0^{e}	2.62 ± 0.29	10 ± 3.4	25 ± 5.7	14 ± 4.2	17 ± 4.7
Stage VI	81 ± 2.5^{e}	143 ± 9.7	81 ± 5.1	102 ± 6.7					
Stage VII	80 ± 2.1	138 ± 7.3	77 ± 4.4	97 ± 5.3					
Stage VIII	74 ± 3.6	122 ± 4.1	69 ± 4.3	81 ± 4.5	2.11 ± 0.17^{a}	8 ± 1.3	20 ± 1.4	11 ± 1.1	13 ± 1.4

Mean values ± SEM. Abbreviations: HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg); CI, cardiac index ($L \cdot min^{-1} \cdot m^{-2}$); MPAP, mean pulmonary arterial pressure (mm Hg); PCWP, pulmonary artery capillary wedge pressure; SPAP, systolic pulmonary artery pressure; PAD, pulmonary artery pressure; stage I, baseline immediately prior to induction; stage II, 3 min after induction, before esmolol; stage III, min 3 of esmolol infusion immediately prior to laryngoscopy/intubation; stage IV, 1 min postintubation; stage V, 3 min postintubation; stage VI, 4 min post intubation, esmolol infusion stopped; stage VII, 5 min after esmolol off; stage VIII, 15 min after esmolol off, prior to incision.

[a] $P < 0.05$ vs group 1. [b] $P < 0.05$ vs group 3. [c] $P < 0.01$ vs group 3. [d] $P \leq 0.05$ vs control. [e] $P \leq 0.01$ vs control. [f] $P \leq 0.001$ vs control.

ginal therapy with propranolol, calcium channel blockers, or nitrates.

Hemodynamic data, both measured and derived, at the various stages of the study are shown in Tables 3 and 4. Six minutes after induction and at minute 3 of esmolol infusion (stage III), the HR in group 3 (72 ± 2.6) was lower than that in the control group (84 ± 3.3). In all three esmolol-treated groups, esmolol attenuated the HR response to induction and intubation (Fig. 2). HR was significantly lower than the control group 1, 3, and 4 min after intubation (stages IV, V, VI); however, 5 min after the esmolol infusion was stopped (stage VII), HR was similar in all groups. HR did not significantly differ among the three esmolol-treated groups at any stage of the study. Systolic blood pressure was significantly lower in esmolol groups than the control after intubation (Table 3). MAP was significantly lower than control in all esmolol-treated groups immediately before intubation (stage III) and in groups 2 and 3 one minute after intubation; however, all groups were similar 5 min after the esmolol infusion was stopped. MAP did not differ among the three experimental groups except in group 2 at stages VI and VIII. Compared to control, the cardiac index in the experimental groups did not significantly differ except in group 1 at stages III and

Table 4. Derived Hemodynamic Measurements

	RPP	SVR	PVR	SVI	LVSWI
Control	(*n* = 10)	(*n* = 5)	(*n* = 5)	(*n* = 5)	(*n* = 5)
Stage I	10792 ± 884	1570 ± 94	121.0 ± 8.5	33.5 ± 1.0	41.6 ± 2.3
Stage II	11834 ± 717	1447 ± 138	136.3 ± 16.6	30.2 ± 3.1	36.3 ± 4.9
Stage III	12087 ± 705	1522 ± 168	143.5 ± 15.3	29.2 ± 1.9	35.9 ± 2.9
Stage IV	19356 ± 856				
Stage V	17534 ± 1093	1554 ± 212	120.4 ± 13.5	28.3 ± 1.9	39.8 ± 4.3
Stage VI	15397 ± 839				
Stage VII	12460 ± 1284				
Stage VIII	9190 ± 673	1510 ± 163	143.1 ± 19.4	24.8 ± 1.7	25.2 ± 1.3
Group 1	(*n* = 10)	(*n* = 4)	(*n* = 4)	(*n* = 5)	(*n* = 4)
Stage I	9931 ± 811	1396 ± 72	130.0 ± 30.0	35.7 ± 39.9	41.5 ± 2.8
Stage II	10537 ± 1065	1183 ± 178	139.7 ± 26.6	33.4 ± 2.8	36.0 ± 2.9
Stage III	9204 ± 953^{c}	1384 ± 290	159.8 ± 32.9	30.5 ± 2.6	27.4 ± 1.1^{b}
Stage IV	14562 ± 1116^{d}				
Stage V	13990 ± 1041^{b}	1417 ± 258	198.5 ± 65.7	33.7 ± 2.5	45.6 ± 3.4
Stage VI	12836 ± 817^{b}				
Stage VII	11411 ± 545				
Stage VIII	9888 ± 731	1290 ± 33	97.6 ± 6.7	34.4 ± 2.4^{b}	35.8 ± 3.3
Group 2	(*n* = 10)	(*n* = 5)	(*n* = 3)	(*n* = 5)	(*n* = 3)
Stage I	10060 ± 706	1271 ± 114	121.7 ± 33.5	39.9 ± 2.4^{b}	43.0 ± 5.5
Stage II	10374 ± 797	1135 ± 85	112.0 ± 26.2	35.5 ± 2.3	34.9 ± 4.1
Stage III	8236 ± 629^{d}	1009 ± 58^{b}	114.0 ± 19.9	33.3 ± 2.7	30.6 ± 4.0
Stage IV	13208 ± 987^{d}				
Stage V	12076 ± 842^{d}	1367 ± 85	131.1 ± 49.3	32.6 ± 2.5	37.1 ± 6.0
Stage VI	11056 ± 745^{c}				
Stage VII	10690 ± 613				
Stage VIII	10697 ± 713^{a}	1405 ± 84	149.6 ± 21.7	30.4 ± 2.3	30.5 ± 1.4
Group 3	(*n* = 10)	(*n* = 4)	(*n* = 4)	(*n* = 4)	(*n* = 4)
Stage I	8978 ± 859	1460 ± 122	120.0 ± 18.0	35.5 ± 3.8	34.4 ± 5.4
Stage II	9637 ± 938	1222 ± 88	94.1 ± 13.2	36.0 ± 2.4	36.4 ± 3.2
Stage III	7656 ± 634^{d}	1103 ± 72	95.6 ± 15.5	34.9 ± 1.8	30.2 ± 1.6
Stage IV	12614 ± 926^{d}				
Stage V	11601 ± 911^{d}	1414 ± 226	127.8 ± 49.6	32.7 ± 4.5	35.8 ± 4.2
Stage VI	11787 ± 1077^{c}				
Stage VII	11059 ± 798				
Stage VIII	8448 ± 668	1753 ± 177	138.3 ± 22.4	30.1 ± 3.9	35.3 ± 4.6^{b}

Mean values ± SEM. Abbreviations: SVR, systemic vascular resistance (dynes·sec·cm^{-5}); PVR, pulmonary vascular resistance (dynes·sec·cm^{-5}); RPP, rate pressure product; SVI, stroke volume index (ml·beat^{-1}·m^{-2}); LVSWI, left ventricular stroke work index (gm·m·m^{-2}); stage I, baseline immediately prior t induction; stage II, 3 min after induction, preesmolol; stage III, min 3 of esmolol infusion immediately prior to laryngoscopy/intubation; stage IV, 1 min post intubation; stage V, 3 min post intubation; stage VI, 4 min post intubation, esmolol infusion stopped; stage VII, 5 min after esmolol off; stage VIII, 15 mi after esmolol off, prior to incision.

[a] $P < 0.05$ vs group 3. [b] $P \le 0.05$ vs control. [c] $P \le 0.01$ vs control. [d] $P \le 0.001$ vs control.

VIII. The rate–pressure product was significantly lower than control in all esmolol-treated groups at stages III, IV, V, and VI, and all groups were similar at stage VII. Except for occasional instances, there were no significant differences between groups at any stage in the derived variables of SVR, PVR, SVI, or LVSWI (Table 4). There were no arrhythmias in any group and one patient in each of the four groups developed ischemia during the study period. There were no adverse effects attributed to esmolol infusion.

The effect of preoperative drug therapy was examined: patients treated with chronic propranolol therapy had lower heart rates, 65.8 ± 3.0 (SEM), $P <$ 0.05, compared with patients not given propranolol 73.2 ± 2.1, at baseline. However, at all other stages chronic propranolol therapy had no effect on HR, an there were no differences at any stage in the othe measured hemodynamics. Additionally, the baselin HR or HR immediately prior to laryngoscopy and intubation had no effect on the HR response thereafter Linear regression analysis demonstrated an association ($r = 0.45$, $P = 0.02$) between the increases i heart rate increase and increase in plasma norepinephrine levels after intubation in the control group however, there was no association between increase in HR and NE in the esmolol-treated groups. Plasm

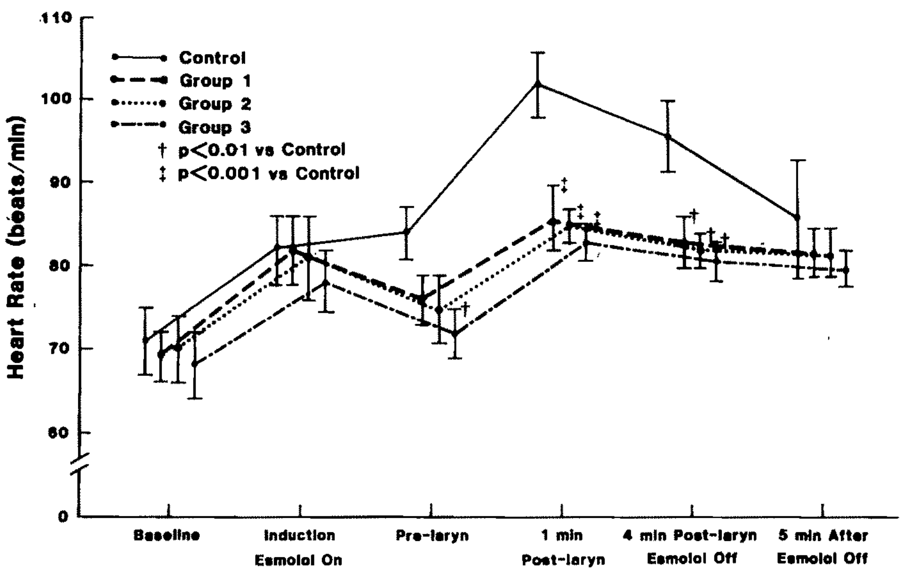

Figure 2. Heart rate responses to laryngoscopy and intubation.

NE levels did not differ between groups at baseline and in all groups tended to decrease with induction and increase with intubation (Table 5). Blood esmolol levels are shown in Table 5. Esmolol levels in groups 2 and 3 were significantly greater than in group 1 immediately prior to laryngoscopy (stage III) and 3 min after laryngoscopy/intubation (stage V) and were significantly higher in group 3 than group 2 only at stage III. Esmolol levels were very low at minute 25 (stage VIII), when only four of the 30 patients had detectable levels of esmolol, one in both groups 1 and 2 and two in group 3. We calculated the time required for the peak plasma drug concentration to decrease by half in four patients with detectable levels at stage VIII and the mean value was 10.5 min.

Discussion

The purpose of this study was to determine the dosage of esmolol that is safe and effective in attenuating the cardiovascular responses to laryngoscopy and tracheal intubation in anesthetized humans. The use of diazepam, nitrous oxide, and pancuronium bromide to induce anesthesia in patients having myocardial revascularization surgery was chosen because safe (11) transient increases in heart rate and blood pressure are known to occur with intubation (11,12). In the present study, it was found that with induction, HR increased and the MAP and CI remained relatively stable. Within each group, HR was significantly greater at stage II (after induction) than at stage I (prior to induction). This presumably is a result of pancuronium, which increases HR (13). The measured hemodynamics after induction were similar to those of previous investigators (12,14,15) and reflect the general hemodynamic stability of this method of induction of anesthesia.

In the experimental groups, the effects of esmolol were seen before laryngoscopy (stage III): heart rate tended to be lower than in the control group. Possible explanations for this are that by blocking β-adrenoceptors there is a decrease in HR, or esmolol attenuates the increase in HR usually seen with pancuronium bromide, or both. The effect of esmolol on the HR was even more pronounced after intubation, the increase in the esmolol-treated groups being approximately one-half of the increase of the control group. The presumed mechanism of this attenuation of HR response is β-adrenergic blockade. This is supported by the fact that plasma levels of NE increased in all groups with intubation, which is evidence of sympathoadrenal response to intubation. There was an association between changes in heart rate and norepinephrine in the control group, but not in the treated groups: this may be interpreted as evidence of β-adrenoceptor blockade of NE effect. Although the course of responses of HR and MAP to induction and laryngoscopy/intubation in this study, as in others (3,4), seems to be directly related to the level of adrenergic activity, esmolol, by blocking the β_1 receptor effects of a generalized increase in sympathetic activity, attenuates the HR response while having little effect on the peripheral manifestation of increased adrenergic stimulation. This effect of esmolol is different from that of propranolol which, because propranolol produces nonspecific β-adrenergic blockade,

Table 5. Plasma Esmolol (ng/ml) and Norepinephrine (pg/ml) Concentrations

	Baseline (preinduction)	Before laryngoscopy (min 3 of esmolol infusion)	3 min after laryngoscopy (min 6 of esmolol infusion)	15 min after esmolol infusion
Control				
ES	NM	NM	NM	NM
NE	241.5 ± 53.3	145.5 ± 36.6	194.3 ± 23.7	NM
Group 1				
ES	NM	1248 ± 115	1154 ± 119	63 (*n* = 1)[g]
NE	262.4 ± 16.8	164.1 ± 16.9	364.8 ± 53.1[d,e]	NM
Group 2				
ES	NM	2359 ± 365[b]	2355 ± 167[b]	421 (*n* = 1)[g]
NE	264.3 ± 55.4	264.1 ± 39.4[a,d,f]	306.0 ± 57.1	NM
Group 3				
ES	NM	4878 ± 481[b,c]	2821 ± 338[b]	758 ± 130 (*n* = 2)[g]
NE	266.7 ± 99.8	96.7 ± 11.7	159.8 ± 45.2	NM

Mean values ± SEM. Abbreviations: ES, esmolol; NE, norepinephrine; NM, not measured.
[a] $P < 0.05$ vs group 1. [b] $P < 0.0001$ vs group 1. [c] $P < 0.0001$ vs group 2. [d] $P < 0.01$ vs group 3. [e] $P < 0.05$ vs control. [f] $P < 0.01$ vs control. [g] All others had nondetectable values 15 min after termination of infusion.

not only attenuates the increase in HR and RPP in response to stimuli (16), but also may increase systemic vascular resistance (17,18).

Myocardial oxygen consumption (MV_{O_2}) was not measured in our patients, but the RPP is a good correlate of overall MV_{O_2} (19), and esmolol significantly attenuated the increase in RPP in all treated groups. Thus it is presumed that esmolol decreased MV_{O_2} in these patients. Although the RPP does not predict regional myocardial supply–demand relationships, examination of the individual components (HR and blood pressure) is useful in management of ischemic heart disease (20). Comparison of the increase in RPP in the esmolol-treated groups with the control group, reveals that increases in RPP were more a result of an increase in blood pressure rather than HR in esmolol-treated patients. This state is more compatible with equalizing oxygen supply and demand rather than having greater increases in HR, as seen in the control group. An increase in blood pressure without a change in HR appears to be better for myocardial oxygenation than an increase in HR along with the increase in blood pressure (21). Despite these theoretical advantages of esmolol, ST-segment changes compatible with ischemia occurred in one patient in each group in the present investigation.

A surprise finding in this study was the absence of an esmolol dose-dependent effect despite significantly different blood levels with the three different esmolol infusion schemes. Sum et al. found dose-related (50, 150, and 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$) differences in attenuating the β-agonist effects of isoproterenol (22). The findings in the present study might be explained by lower dosages maximally blocking the β-receptors with no additional blocking action from the higher dosages. Alternatively, although there was a 2.5-fold difference in total amount of esmolol infused in the patients (1100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in group 1 vs 2700 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in group 3), perhaps this is not a sufficiently large enough difference despite a four-fold range in mean plasma blood levels prior to intubation (1248–4878 ng/ml) to produce a dose–effect relationship. Regardless of the reason, we were unable to show a dose-dependent effect of esmolol on hemodynamic variables in anesthetized humans.

The duration of β-adrenergic blockade with esmolol was brief. Five minutes after the cessation of esmolol infusion there was no longer a difference in HR between the esmolol groups and the control group. This relatively short duration of β-adrenergic blockade effect is consistent with laboratory data showing a markedly shorter duration of β-blockade with esmolol compared to propranolol (2). Esmolol effects in that study disappeared in 10–15 min, whereas propranolol effects remained for a much longer time. The short-lived action of esmolol is due to rapid plasma clearance. Esmolol is hydrolyzed by esterases in dog and human blood (23). In healthy awake humans, the distribution and elimination $t_{1/2}$ average 2 and 9 min, respectively (22). In the present study, sampling was not sufficiently frequent to permit pharmacokinetic modeling of blood esmolol data, but the drug was detectable in only 4 of the 30 patients 15 min after cessation of infusion. Assuming a first order decay, the approximate half-life in these four patients was 10.5 min. However, the actual half-life for the entire group was much lower than this value because this mean does not reflect the majority of the cases, in whom the plasma esmolol level was not detectable.

In summary, this is the first study evaluating the cardiovascular effects of various doses of esmolol. Esmolol is safe and effective in attenuating the HR response associated with laryngoscopy and intubation in lightly anesthetized patients undergoing myocardial revascularization surgery. The rapid disappearance of esmolol from the blood paralleled the short duration of HR effect in this study. There are many potential uses for this unique β-adrenergic blocker in the perioperative period.

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Effects of Low Doses of Meperidine on Neonatal Behavior

Betty R. Kuhnert, PhD, Patricia L. Linn, PhD, Mary J. Kennard, CPNP, and
Paul M. Kuhnert, PhD

KUHNERT BR, LINN PL, KENNARD MJ, KUHNERT PM. Effects of low doses of meperidine on neonatal behavior. Anesth Analg 1985;64:335–42.

After meperidine administration during labor, meperidine reaches its highest level in fetal tissues within 2–3 hr. The highest levels of normeperidine, the active metabolite of meperidine, are, on the other hand, determined in fetal tissues by the time between administration of meperidine to the mother and delivery: the greater the drug-to-delivery interval (DDI), the higher the fetal levels of normeperidine. Because of the different times to peak fetal levels of meperidine and normeperidine, it may be possible to partially separate the effects of meperidine and its metabolite on the neonate using the DDI. The purpose of this study was to determine whether low doses of meperidine affected performance on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), and whether this performance is related to the DDI or to levels of meperidine or to normeperidine. Sixteen control neonates whose mothers received no meperidine and 41 study infants whose mothers received 25–100 mg meperidine intravenously (mean 39 ± 19 mg) were studied. Comparisons of BNBAS scores of control and study infants measured at < 12 hr, again at 3 days of age, and the effect of DDI were made using repeated measures analyses of variance (ANOVA). Correlation techniques were used to examine relationships between BNBAS performance and clinical and pharmacological variables related to drug administration. The BNBAS cluster scores representing regulation of state and number of abnormal reflexes were significantly different in study neonates from control neonates. Performance depended upon test day. Further analysis showed that longer DDIs resulted in less optimal BNBAS performance. The number of abnormal reflexes was significantly related to the DDI at both test times. Longer DDIs resulted in more abnormal reflexes. Cord venous pH and maternal parity were significant covariates. These results suggest that even low doses of meperidine may influence neonatal behavior. Furthermore, the difference in BNBAS scores suggests that less optimal performance with longer DDIs may be caused by normeperidine.

Key Words: ANESTHESIA—obstetric. ANALGESICS—meperidine.

Meperidine (Demerol) is widely used as a narcotic analgesic in obstetrics (1). It is known to cross the placenta, reach the fetus, and appear in breast milk (2–4). Furthermore, meperidine has a pharmacologically active metabolite, normeperidine, which may also affect the fetus (4). Although meperidine has been used in obstetrics since 1939, neither its pharmacology nor its effects on neonatal neurobehavior has been fully elucidated.

The study of the pharmacology of meperidine was hampered until the 1970s by the lack of suitable analytical techniques. In 1971 O'Donoghue administered meperidine to neonates of untreated mothers and showed that neonates could metabolize meperidine within 24 hr after birth (5). She was able to identify meperidine, normeperidine, and meperidinic acid in urine from these neonates. Her results showed that the neonate had a much greater ability to metabolize drugs than was thought previously, and that this ability increased substantially within the first 72 hr after birth. Subsequent studies documented the appearance of normeperidine in maternal plasma during labor (6) and in cord blood (7,8), and verified the presence of normeperidine in neonatal urine (7,9). It is now well accepted that the neonate can produce normeperidine, but at a much slower rate than the mother (5,9). Studies of the disposition of meperidine at birth have shown that cord blood levels decrease with time from administration of the drug to the mother (7), but that meperidine reaches its highest level in fetal tissues within 2–3 hr after administration to the mother (7,10). Studies of the disposition of normeperidine at birth have shown that cord blood levels increase with time from administration to the mother,

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Address correspondence to Dr. Betty R. Kuhnert, Department of Obstetrics and Gynecology, Cleveland Metropolitan General Hospital, 3395 Scranton Road, Cleveland, OH 44109.

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and that normeperidine reaches its highest level in fetal tissues with longer drug-to-delivery intervals (DDI) (7). Levels of normeperidine in neonatal tissues are related to both the levels of meperidine present in neonatal tissues at birth and to the drug-to-delivery interval (7). In the neonatal period, the half-life of meperidine is 13 hr; whereas the half-life of normeperidine is 62 hr (11). Thus after the first day of life, normeperidine levels are higher than meperidine levels in both plasma and urine (11).

It is known that large doses of meperidine given to the mother during labor can increase neonatal morbidity. Large doses have been related to respiratory depression (10,12,13), lowered Apgar scores (14), less than optimal acid–base status (13), and EEG irregularities (15,16). Moreover, neonatal morbidity is greater when the mother is given meperidine 2–3 hr before delivery (4,16). If the drug is given closer to delivery, the adverse effects are fewer (4). These studies (4,16) suggest that normeperidine may be the reason for the differences in neonatal effects related to differences in time between meperidine administration and delivery of the infant.

Studies of more subtle indices of neonatal neurobehavior have reported positive, negative, and marginal effects of meperidine. Differences in psychophysical effects such as decreased looking times (17) and longer habituation rates (18,19) have been reported in meperidine-exposed vs control infants. Using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) (20) or modification thereof, less optimal performance has been reported when meperidine was combined with epidural anesthesia (18), or meperidine was combined with other drugs (21); whereas no effects of meperidine plus anesthesia (22) or low doses of meperidine alone (23) have been reported for the neonate. Indeed, more optimal neonatal performance has been reported after administration of meperidine to the mother (24). Using the Scanlon test (25), generalized depression of neonatal test scores during the first three days of life has been reported in a series of studies (26–28). Using other behavioral measures, researchers have concluded that meperidine has a deleterious effect on sleep–wake and activity cycles (29), newborn feeding (30), and possible effects on infant–caregiver interactions (31). From most of these studies it appears that meperidine plus other obstetrical medications may affect certain aspects of newborn behavior. Many of the previously mentioned studies are, however, incomplete so that more specific statements about the effect of meperidine on neonatal outcome cannot be made.

Many of the earlier studies are incomplete or irrelevant to today's practice of obstetrics for several reasons. First, the dosages of meperidine given to laboring women are much lower today. In early studies, increases in neonatal morbidity after doses of 200 mg or more to the mothers were reported (10). Today doses of 75 mg or less are more common (32). Second, a combination of several drugs often was administered to laboring women in the early studies (18,21,22). The practice of combining drugs with different pharmacological actions with unstandardized dosage or potency scores, or attempting to control the effects of multiple drugs without considering possible synergistic or antagonistic drug interactions precludes the definition of meperidine effects (30). Third, few studies have included data on the levels of meperidine in the infant at birth and none have reported normeperidine levels. The lack of specific pharmacological data appears to be the most common flaw of this area of research (25). Fourth, appropriate nonmedicated control groups were often lacking (25). Finally, very few studies have included information regarding the time interval between administration of the drug to the mother and delivery of the infant. This information is important because neonatal morbidity has been found to be related to DDI (4,16). Furthermore, meperidine reaches a peak in neonatal tissues at a 2–3 hr DDI and normeperidine reaches a peak much later (7,10). The purpose of this study was to determine whether low doses of meperidine given intravenously during labor affect performance on the BNBAS (20) and whether this performance is related to the DDI or levels of meperidine, normeperidine, or both.

There is a variety of measures designed to assess newborn functioning and the choice of the BNBAS for this study was based on a number of considerations. For example, some tests are more useful after one month of age, others are intended for use immediately after birth, and others are limited to assessment of only one aspect of newborns' function (33). The BNBAS includes items descriptive of many aspects of neonatal behavior including reflexes, physiological responses to certain stresses, irritability–consolability, and social–interactive behavior with the caregiver. The BNBAS is the most widely used measure of newborn behavior and is well standardized (34). Therefore, the BNBAS was selected as the outcome measure for this study.

Methods and Materials

Fifty-seven healthy parturients at term with uncomplicated pregnancies or labors who vaginally delivered normal, healthy infants were included in this study. The study was approved by the Human Investigation Committee of Cleveland Metropolitan

General Hospital, and informed consent was obtained in early labor from each mother. Forty-one mothers were given meperidine intravenously for analgesia during labor, plus, in some cases, perineal infiltration of local anesthetic for delivery but no other medication for relief of pain prior to delivery of the infant. Sixteen mothers delivered without medication.

Clinical characteristics were recorded for each pregnancy. These included maternal antenatal characteristics—age, race, gravidity, parity, and length of labor; and neonatal characteristics—gestational age as determined by the Ballard modification of the Dubowitz examination (35), Apgar scores at 1 and 5 min, birth weight, cord venous pH (in 14 control and in 24 study infants), and sex.

Pharmacological data were recorded for each mother. These included the number of doses and the total dose of meperidine administered as well as the DDI for the first and last dose. Concentrations of meperidine and normeperidine in cord venous blood were determined by gas chromatography–mass spectrometry (8) in 22 of the infants.

Examinations using the BNBAS were performed by one of two trained examiners who were blind to maternal history. Infants were examined within their first 12 hr and at 3 days of age. All examinations were done midway between feedings, when the infants were expected to be sleeping. Reliability between the two examiners was checked and found to be 94%. Reliability was also monitored by periodically sending each of the examiners to Dr. Brazelton's laboratory for reexamination during the 5 yr study period (1977–1982). Neonatal neurobehavioral performance was scored using the seven a priori behavioral clusters suggested by Lester et al. (36). These include clusters of the habituation, orientation, motor, range of state, regulation of state, autonomic regulation and number of abnormal reflexes.

The analysis plan was designed to answer two major questions. First, did the infants exposed to meperidine differ from the no-drug control infants on their Brazelton cluster scores? To address this question, the two Brazelton tests of the meperidine-exposed infants were compared with the tests of the no-drug control infants using a repeated measures analysis of variance (ANOVA). This analysis was designed to determine whether the Brazelton scores were affected by meperidine; the time when BNBAS scores were tested; or a combination effect (or "interaction") of meperidine and time of BNBAS exam. For example, if the study group performed better than the control group on the first exam, but worse on the second, this would be an interaction effect.

The second question that was asked was: did the DDI affect the BNBAS scores? This question was asked only for those clusters affected by the drug. To answer this question the subjects in the study group were divided into three groups based on their DDI, and the repeated measures ANOVA was used with this grouping of subjects. Here significant effects of the DDI group on the BNBAS scores were of interest.

Classifying subjects into study vs control groups, or short, medium, or long DDIs does not take advantage of the fact that the amount of drug in the infant's system and the DDI are continuous variables. We wondered whether there was a linear relationship between drug levels and BNBAS scores, or between the number of minutes from drug administration to delivery and the scores. These questions and the relationship between infant pH (another continuous variable) and the BNBAS scores were studied by correlation techniques. If the information was available for a sufficient number of patients (e.g., DDI), stepwise regression was used so that variables like parity and length of labor could be controlled. If the information was only available for few of the patients, (i.e., pH and drug levels), then only simple correlations were used. $P < 0.05$ was accepted as statistically significant.

Table 1. Pharmacological Characteristics ($n = 41$)

Meperidine	Mean ± SD	Range
No. doses administered	1.2 ± 0.6	1–3
No. mg administered	39 ± 19	25–100
DDI (min)	124 ± 99	8–400

Results

Fifty-seven infants were studied. Each infant was tested in the first 12 hr of life, at 3 days of age, or both. Forty-seven infants had both BNBAS examinations. Table 1 summarizes the pharmacological variables. It can be seen that the amount of meperidine administered to these patients was very low. Twenty-three patients received 25-mg doses, and fourteen received 50 mg. Only one patient received 100 mg. All but six of the patients received single 25- or 50-mg doses. The time interval between administration of the drug and delivery ranged from 8–400 min.

The clinical characteristics of the mothers and neonates are shown in Tables 2 and 3. All mothers were healthy and had normal labors and vaginal deliveries. The parity of control mothers was significantly greater than the parity of the study mothers ($t = 2.94$, $P < 0.01$) and control mothers had significantly shorter labors ($t = 2.6$, $P < 0.01$) than the study group. Twenty-

Table 2. Clinical Characteristics of Study and Control Mothers

Characteristics	Study group (n = 41)	Control group (n = 16)
Gravidity	2.2 ± 1.0 (1–5)	3.5 ± 1.8^a (1–7)
Parity	0.7 ± 0.8 (0–4)	1.7 ± 1.3^a (0–5)
Age (yr)	22.0 ± 4.7 (16–36)	21.8 ± 4.3 (15–32)
Length of labor (hr)	10.6 ± 4.7 (3–26.5)	7.1 ± 4.4^a (0.23–14.4)
Local perineal infiltration		
None	20	16
Lidocaine	20	0
Chloroprocaine	1	0

Values given as mean ± SD (range).
$^a P < 0.01$ by t-test.

Table 3. Clinical Characteristics of Study and Control Neonates

Characteristics	Study group (n = 41)	Control group (n = 16)
Gestational age (weeks)	39.5 ± 1.2 (37–42)	39.3 ± 1.5 (38–42)
Birthweight (g)	3282 ± 430 (2580–4900)	3113 ± 359 (2700–3900)
Apgar < 7 at 1 min (n)	2	2
Apgar < 7 at 5 min (n)	0	0
Sex (n)		
Male	21	5
Female	20	11

Values given as mean ± SD (range).

one of the 41 women (51%) receiving meperidine, but none of the 16 control mothers, required local perineal infiltration for episiotomy. All of the pregnancies had good outcomes. Only two infants in each group had 1 min Apgar scores less than 7 (one 2 and one 5 in each group). There were no 5-min Apgar scores less than 8. One control and two study infants had a cord venous pH less than 7.25 at delivery.

Table 4 shows the mean, standard deviation, and range of meperidine and normeperidine cord vein plasma levels for the 22 study infants with samples available for laboratory analysis. All 22 of the infants had detectable meperidine levels; twelve had detectable normeperidine levels. Normeperidine, but not meperidine, was found to be significantly and positively correlated with the DDI (Pearson correlation coefficient 0.53, $P < 0.05$).

Table 4. Meperidine and Normeperidine Cord Venous Plasma Levels (ng/ml) in Infants (n = 22)

Drug	Mean ± SD	Range
Meperidine	94.5 ± 51.6	40–221
Normeperidine	7.7 ± 9.1	0–32^a

^{a}Detectable in 12 of 22 samples.

To determine whether there were differences between the control and study groups, a series of 2 (study vs control group) × 2 (< 12 hr vs 3 day exam) repeated measures ANOVAs was conducted for each of the seven BNBAS clusters (36). These included habituation, orientation, motor, range of state, regulation of state, autonomic regulation, and number of abnormal reflexes. Because the control and study group mothers were significantly different in terms of parity, need for episiotomy, and length of labor, these variables were considered possible covariates. That is, it was desirable to control for these factors in studying the group differences, to be more certain that it was the drug or control group status of the mothers that was influencing the BNBAS scores. Only parity showed a significant correlation with the BNBAS scores, and so parity was used as a covariate in the ANOVAs. Significant effects of the time of BNBAS testing were found for the orientation ($F(1,46) = 4.32$, $P < 0.05$), motor ($F(1,46) = 11.96$, $P < 0.001$), and autonomic regulation ($F(1,46) = 4.27$, $P < 0.05$) clusters. For all three clusters, the infants showed improved performance on the second test.

No significant effects of meperidine alone were found. However, significant interaction effects of time of test and meperidine were found for two clusters: regulation of state ($F(1,46) = 4.62$, $P < 0.04$) and reflexes ($F(1,46) = 3.87$, $P < 0.05$). These interactions are shown in Figures 1 and 2. In both cases, analysis of covariance showed that the group differences were not due to parity. For the regulation of state cluster, the drug group had a higher mean score on the first test, but on the second test the groups switched so that the control subjects had the optimal mean score (Fig. 1). (Standard deviations for the study group for the first and second exam were 0.92 and 0.95, respectively; and for the control group, 1.03 and 1.01, respectively). It should be noted that although the mean differences between the groups were significant, the groups differed by less than one scale point on the test and, therefore, the differences may not be clinically meaningful. The reflex cluster is simply the number of abnormal reflexes, so that on this cluster a low score is optimal. Figure 2 shows that the relative position of the drug and control group mean scores also depended on the exam day: the control group had significantly more optimal scores on the first examination, while the drug group's scores are significantly more optimal on the second examination day. (Standard deviations for the study group for the first

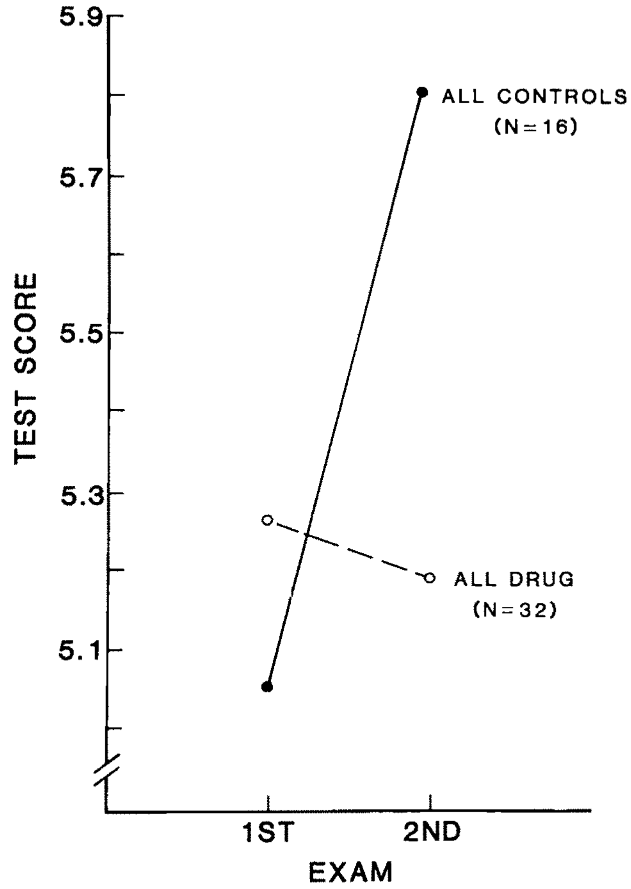

Figure 1. Comparison of mean levels of regulation of state cluster scores for control and drug groups.

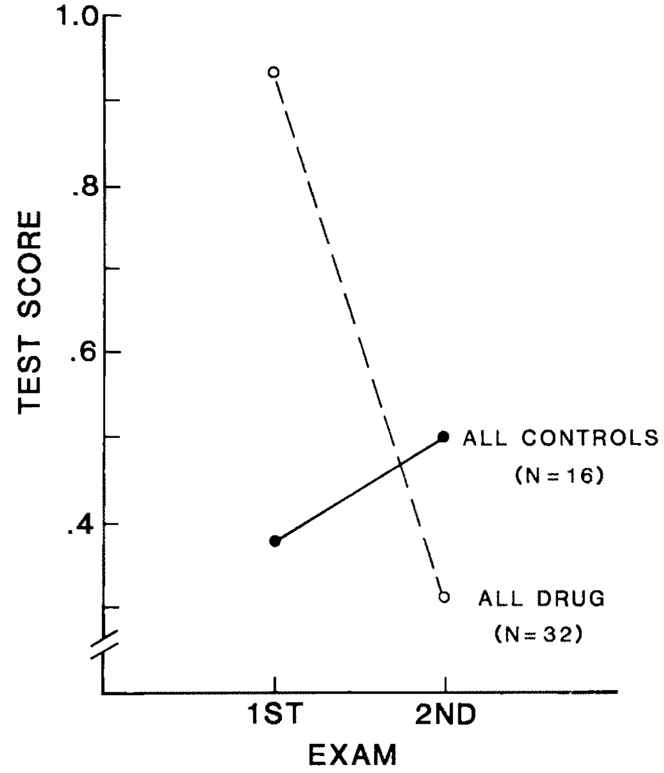

Figure 2. Comparison of mean levels of number of abnormal reflexes for control and drug group.

and second exam were 1.45 and 0.64, respectively; and for the control group, 1.25 and 1.21, respectively.)

The two regulation of state cluster scores and the two reflex cluster scores were then studied further for the drug group only, to determine whether there was a relationship between the scores and the DDI. The subjects were first divided into three groups based on the number of minutes that elapsed between the administration of the meperidine and the delivery of the infant: long (> 3 hr), medium (> 1 hr and < 3 hr), and short (< 1 hr) intervals were studied. A 2 (exam day) × 3 (DDI group) repeated measures ANOVA was then used to determine whether the DDI affected the BNBAS scores. None of these ANOVA analyses revealed a significant difference.

To further explore the relationship between DDI and newborn regulation of state and reflexes, a regression analysis was done to determine whether the DDI and cluster scores were significantly correlated after controlling for the number of doses of meperidine given to the mother, her age, gravidity, and length of labor. For the reflex cluster, the regression analysis showed a significant relationship on both the first ($F(5,28) = 3.90$, $P < 0.01$) and second exam ($F(5,31) = 4.32$, $P < 0.01$). On both examination days, a longer DDI was significantly associated with more abnormal reflexes. This is displayed for the reflex cluster in Figure 3. For this cluster, the group means are ordered; less optimal performance is seen with longer drug-to-delivery intervals. (Standard deviations for the first and second exam were 0.67 and 0.39 for < 1 hr, 0.98 and 0.67 for 1–3 hr, and 2.27 and 0.88 for > 3 hr, respectively.)

Closer examination of scatter plots showed that the results on the first exam were significantly influenced by two neonates in the longest DDI group (DDIs of 218 and 400 min) who had five and six abnormal reflexes, respectively. When these two infants were removed from the analysis, the results from the first exam were no longer significant. The significant effect on the second examination was not due to extreme scores. Maternal gravidity and length of labor were significant covariates for the first and second examination, respectively. This analysis supports a significant relationship between neonatal behavior and DDI.

Because meperidine effects were found most consistently for the reflex cluster score, the raw data were reviewed to determine whether the reflexes were scored as being abnormally hypotonic or hypertonic,

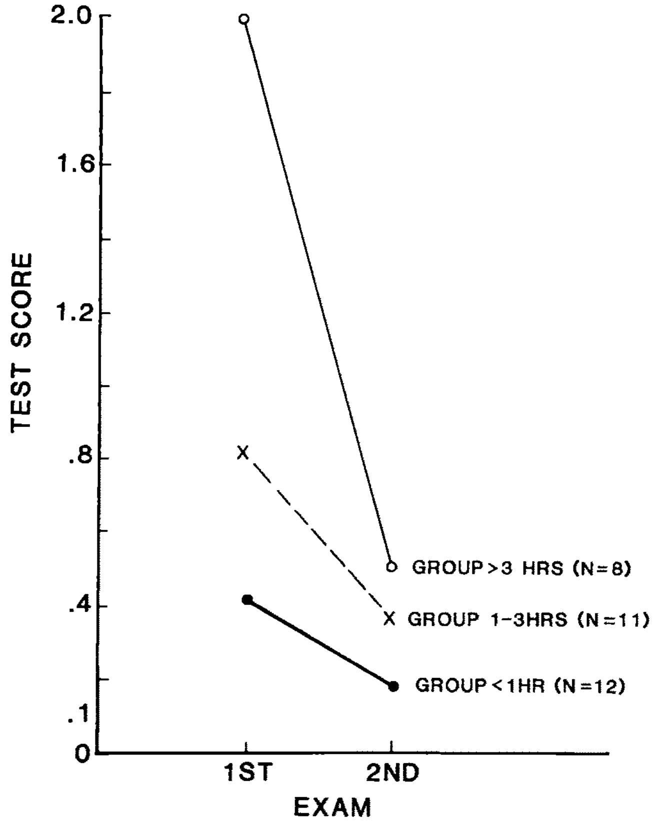

Figure 3. The relationship between the drug-to-delivery interval and the mean number of abnormal reflexes in the meperidine group.

and which reflexes were most frequently scored as abnormal. All of the abnormal reflexes were scored as hypotonic responses as shown in Table 5. The reflexes walking, standing, and placing were most frequently scored as abnormal, especially in the study group on the < 12 hr test.

Analysis of the relationship between DDI and the regulation of state cluster showed a significant relationship on the second testing only ($F(5,31) = 2.651$, $P < 0.05$). Again, a longer DDI was associated with less optimal regulation of state.

No significant relationships could be demonstrated between the cord blood levels of meperidine and normeperidine and the regulation of state or reflex cluster scores using simple correlation analyses. The number of patients with drug levels was too small to do stepwise multiple regression analyses.

Similarly, the number of neonates in the drug group with cord venous pH levels was too small for stepwise multiple regression analyses with several covariates. However, in this case, a significant simple correlation ($r = -0.46$, $P < 0.05$, $n = 21$) was found between the 3-day reflex score and pH. The relationship between the DDI and the 3-day reflex score was not caused by pH, however, because the partial correlation coefficient between reflex and DDI remained significant even when pH was forced in as a control variable.

Discussion

The purpose of this study was to test the hypothesis that low doses of meperidine given intravenously during labor affect performance on the Brazelton Neonatal Behavioral Assessment Scale and that performance would be related to the drug-to-delivery interval and to neonatal cord blood levels of meperidine or normeperidine. This hypothesis was based on clinical reports of increased neonatal morbidity with longer drug-to-delivery intervals (4,16), pharmacological reports of increased fetal tissue uptake of meperidine at 2–3 hr after administration to the mother (7), and increased fetal tissue uptake of normeperidine with longer drug-to-delivery intervals (7,8). The present results suggest that even very low doses of meperidine can have subtle neonatal neurobehavioral effects. Furthermore, with longer drug-to-delivery intervals, these effects are more pronounced. Although no relationship was found with cord vein drug levels, the persistence of effects to 3 days of age supports the possibility that neonatal levels of normeperidine affect neonatal neurobehavior.

Earlier studies often lacked appropriate nonmedicated controls. This study included a control group that was nonmedicated. However, we expected to find that the controls were more parous and had shorter labors than the study mothers. The reason for this is that in shorter labor, usually less analgesia is required. Similarly, more parous women have shorter labors. Statistical techniques that allowed for control of these variables were thus needed to eliminate the effects of these clinical factors on neonatal neurobehavior. Because parity was the only variable that was significantly related to BNBAS scores, parity was used as a covariate in subsequent analyses. Length of labor was not related to test score.

Once the effects of the clinical covariates that are known to affect neonatal outcome were taken into account, it was found that very low doses of meperidine affected neonatal neurobehavior. In particular, regulation of state and the number of abnormal reflexes were affected. In each case, less optimal performance on at least one of the test days was noted. Furthermore, these findings were more apparent in the changes in test scores over time. It would be expected that improvement in test scores would occur as a neonate recovers from the stresses of labor and delivery and adapts to the extrauterine environment. In regards to regulation of state, there was a greater improvement in test scores from the first to the second exam in the control group than in the drug group. In

Table 5. Number of Abnormal Reflexes Found for Study and Control Neonates

	First exam		Second exam	
Reflex	Study group *n* (%)	Control group *n* (%)	Study group *n* (%)	Control group *n* (%)
Standing	8 (22)	1 (6)	3 (8)	2 (13)
Automatic walking	9 (25)	1 (6)	3 (8)	3 (19)
Placing	3 (8)	1 (6)	1 (3)	2 (13)
Crawling	3 (8)	1 (6)	—	1 (6)
Incurvation	4 (11)	2 (13)	1 (3)	—
Nystagmus	1 (3)	—	2 (5)	—
Rooting	2 (6)	—	—	—
Sucking	1 (3)	—	—	—
Hand	1 (3)	—	—	—
Ankle	1 (3)	—	2 (5)	—
Babinski	—	—	1 (3)	—

No neonates in either group were found with abnormal tonic deviation of head and eyes, tonic neck, or moro reflexes or abnormal passive movements of the arms or legs.

regards to the number of abnormal reflexes, there was a large improvement in the drug group, and the scores were similar to the controls on the second exam. These findings disagree with a previous study in which no effects of low doses of meperidine vs no medication could be found (23). It is important to note that the reflexes most affected were walking, standing, and placing rather than reflexes that could affect feeding, such as sucking and rooting.

The results of this study only indirectly support the hypothesis of adverse effects due to the meperidine metabolite, normeperidine. The relationship on both days between DDI and number of abnormal reflexes supports involvement of normeperidine. This is because with longer drug to delivery intervals, infants have more normeperidine in their tissues at birth. This was seen in the present study and has been reported previously (7,8). Furthermore, this is supported by recent studies showing that both neonatal urine and plasma levels of normeperidine at three days of age are considerably greater than meperidine levels (7,9,11). For example, neonatal plasma normeperidine levels may be 2–100 times higher than meperidine plasma levels at 3 days (11). However, we found no direct correlation between meperidine or normeperidine levels at birth and neonatal outcome in the present study. It may be that drug levels at birth are not representative enough of body burden of drugs and that drug levels obtained closer to the time of exam would be more predictive of neurobehavioral scores. The hypothesis of the involvement of a metabolite needs to be tested by obtaining meperidine and normeperidine levels at the completion of each neurobehavioral examination.

With longer labors, infants tend to become acidotic. Therefore, it is hard to distinguish between the effects of the DDI and pH on neonatal neurobehavior. However, there was a statistically significant effect in this study of DDI independent of pH. This was most obvious with the reflex cluster, where pH was forced into the regression equation and the DDI–reflex relationship was still significant. It should be noted that two infants in the longest DDI group had 5 or more abnormal reflexes at birth. Most of the others had 0–2 abnormal reflexes at delivery and fewer at 3 days of age. Nevertheless, lower BNBAS scores with longer drug-to-delivery intervals were still apparent at 3 days of age.

The results of this study suggest that there are neurobehavioral responses associated with very low levels of meperidine in normal healthy infants, but that they are subtle. The only differences noted in performance between the study and control groups were in the regulation of state and reflex clusters. The differences between means of the scores on the regulation of state cluster were less than one scale point. Horowitz et al. (37) and others have suggested that differences of one scale point or more are necessary to be considered meaningful. The number of abnormal reflexes reflect brainstem functioning that may not be apparent to the caregiver. However, the items in the regulation of state cluster include cuddliness, consolability, self-quieting, and hand-to-mouth activity. Any of these behaviors could influence caregiver–infant interactions. Early social interactions may then influence infant development (38), and thus even subtle drug effects on the infant should be considered when drugs are administered during labor and delivery.

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Accumulation of Methane, Acetone, and Nitrogen in the Inspired Gas during Closed-Circuit Anesthesia

Shigeho Morita, MD, William Latta, MD, Kate Hambro, RN, and
Michael T. Snider, MD, PhD

MORITA S, LATTA W, HAMBRO K, SNIDER MT. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. Anesth Analg 1985;64:343–7.

During closed-circuit anesthesia, the patient's inspired gas may become progressively contaminated by nonanesthetic gases. We studied the concentrations of methane, acetone, and nitrogen as nonanesthetic gas contaminants in the circuit gas of 16 cases during closed-circuit anesthesia. After a "short" period of denitrogenation (6–8 min), average nitrogen concentration in the closed circuit increased from 6.4 to 16.2%, methane from 4.3 to 22.4 ppm, and acetone from 0.3 to 2.2 ppm. After "long" denitrogenation (33 min), average nitrogen concentration in the closed circuit increased from 1.0 to 5.1%, methane from 3.7 to 17.9 ppm, and acetone from 1.3 to 5.9 ppm. It is concluded that gases stored in tissues or produced within the body can appear in the patient's expired gas during closed-circuit anesthesia. Intermittent flushing of the circuit with high flow gases is suggested to remove these contaminants.

Key Words: ANESTHETIC TECHNIQUES—closed circuit. EQUIPMENT—CIRCUITS, closed.

Closed-circuit anesthesia has been proposed as an inexpensive but effective means of reducing air pollution by anesthetic gases in the operating room (1). Although keeping anesthetic gases and vapors within the circuit prevents their inhalation by the personnel in the operating room, the patient's inspired gas may become progressively contaminated by nonanesthetic gases. Nitrogen (2), volatile metabolic products of halothane (3), and carbon monoxide (4) have been detected during closed-circuit anesthesia.

Pharmacokinetic theory suggests that the vapor of any volatile liquid contaminating the fresh gas inflow, stored in the anesthetic apparatus of patients' tissues, or produced within the patients' body can appear in the inspired gas during closed-circuit anesthesia. Using gas chromatography we monitored the circuit gas of 16 patients for the appearance and accumulation of methane, nitrogen, and acetone during routine closed-circuit anesthesia. Flushing the circuit with high-inflow fresh gas was evaluated as a means of reducing the accumulated contaminants.

Methods

Anesthesia Circuit

All patients breathed gas mixtures from an anesthesia machine (Ohio 5333 EFP), the inspiratory and expiratory ports of which were fitted with corrugated polyethylene tubing. Inspired gases passed through a Cascade 1 Model Humidifier. The circuit had no leak at a static pressure of 60 cm water. Parallel rotameter flow meters permitted oxygen and nitrous oxide inflows to be accurately measured at rates from 10 to 8000 ml/min. Halothane or enflurane, when used, were injected as a liquid directly into the expiratory limb or delivered as vapor by an out-of-circle Copper Kettle.

Anesthetic Protocol

We took measurements in 16 ASA physical status I or II patients undergoing routine clinical closed-circuit anesthesia for a variety of abdominal or peripheral operations.

Series 1—Short denitrogenation. This series used a high-flow semi-closed system for 6–8 min before the circuit was closed. In nine patients, denitrogenation with 100% oxygen was carried out for 3 min prior to anesthetic induction with thiopental and tracheal intubation facilitated by succinylcholine. After intuba-

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Address correspondence to Dr. Morita, Department of Anesthesia, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113 Japan.

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tion and during mechanical ventilation, 30% oxygen and 70% nitrous oxide with a total flow of 5 L/min were given until the expired oxygen read 30% by a polarographic analyzer (Foregger 450). This required 3–5 min. The circuit was then closed and oxygen and nitrous oxide flows were adjusted to keep both the expired oxygen concentration and reservoir bag volume constant. Circuit gas was sampled at the time the circuit was closed and again 10, 20, 40, 80, and 160 min later according to the duration of surgery.

Series 2—Long denitrogenation. This series used a high-flow semi-closed system for 33 min before the circuit was closed. Seven additional patients were denitrogenated with 100% oxygen, then anesthetized with thiopental and intubated with the aid of succinylcholine. Patients were then ventilated with 30% oxygen and 70% nitrous oxide via a semiclosed system with a total flow of 5 L/min for 30 min prior to closing the circuit. Again, oxygen and nitrous oxide flows were adjusted to keep the expired oxygen concentration at 30% and reservoir bag volume constant. Circuit gas was sampled at the time the circuit was closed and again 10, 20, 40, 80, 120, 160, 240, and 320 min later, according to the duration of surgery. When inspired concentrations of nitrous oxide were found to be less than 50% by gas chromatography, supplemental thiopental, halothane, or enflurane was given to prevent awareness. In five patients we flushed the circuit at the end of the surgery with fresh anesthetic gases at 6 L/min for 2 min. Measurement of circle gases 2 min later allowed us to evaluate flushing as a means of reducing accumulated contaminant gases.

Chromatography

Circuit gas samples were analyzed for nitrogen, oxygen, nitrous oxide, and carbon dioxide by gas chromatography using a thermal conductivity detector. Two-milliliter samples of gas were injected into a helium carrier stream flowing at 20 ml/min and separated at room temperature on either a 13 × molecular sieve or a Porapak Q column. Both were 112 cm long and 6.4 mm in diameter. The Porapak Q column separated carbon dioxide and nitrous oxide; the sieve separated nitrogen and oxygen. To measure acetone and methane we used a flame ionization detector. For methane analysis, 1-ml samples of gas were injected into a helium carrier stream flowing at 10 ml/min and separated at room temperature on a Porapak T column 180 cm long and 3.2 mm in diameter. For acetone analysis, the same column was heated to 160°C and the carrier flow increased to 30 ml/min. Room air and gravimetric standard gases were used to calibrate detectors for nitrogen, oxygen, nitrous oxide, carbon dioxide, methane, and acetone.

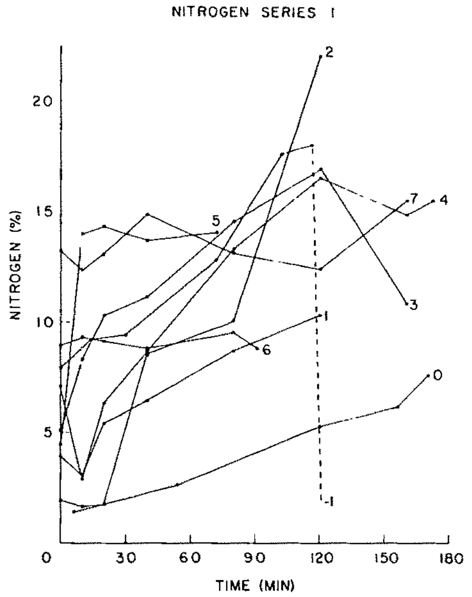

Figure 1. When a high-flow semi-closed system was used for only 6–8 min prior to circuit closure (Series I), the average circuit nitrogen concentration increased from 6.4 to 16.2% during 120 min of closed-circuit anesthesia.

Results

In Series I (short denitrogenation) the average nitrogen concentration increased from 6.4% at circuit closure to 16.2% at 120 min (Fig. 1). In six patients, the average methane concentration increased from 4.3 to 22.4 ppm at 120 min. In one patient, the concentration of methane reached 229 ppm after 72 min. Average acetone concentration increased from 0.3 ppm at 0 min to 2.2 ppm at the end of the case.

In Series II (long denitrogenation) the average nitrogen concentration increased from 1.0% at circuit closure to 5.1% at 120 min (Fig. 2). The average methane concentration increased from 3.7 ppm at 0 min to 17.9 ppm at 120 min (Fig. 3). Average acetone concentration increased from 1.3 ppm at 0 min to 5.9 ppm at the end of the case (Fig. 4). In five cases (3–7), flushing the anesthesia circuit with fresh gases for 2 min at 6 L/min produced a dramatic decrease in methane and nitrogen concentration in the circuit (Figs. 2, 3), but decreased the concentration of acetone only minimally (Fig. 4).

Discussion

Any volatile compound or gas that can wash out from body tissue stores, wash out from production sites in the body tissues or bacterial flora of the bowel, con-

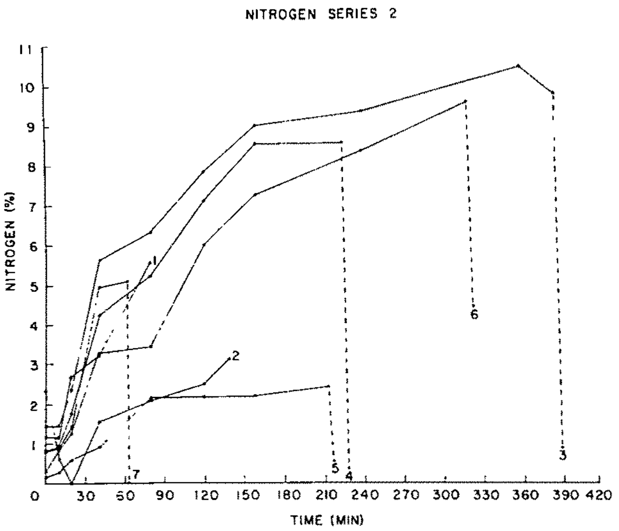

Figure 2. With a high-flow semi-closed system in use for 33 min prior to circuit closure (Series II), the average nitrogen concentration was reduced to 1.00% when the circuit was closed and increased to 5.13% after 120 min of closed-circuit anesthesia. Flushing the circuit with fresh anesthetic rapidly decreased the nitrogen level (dotted lines).

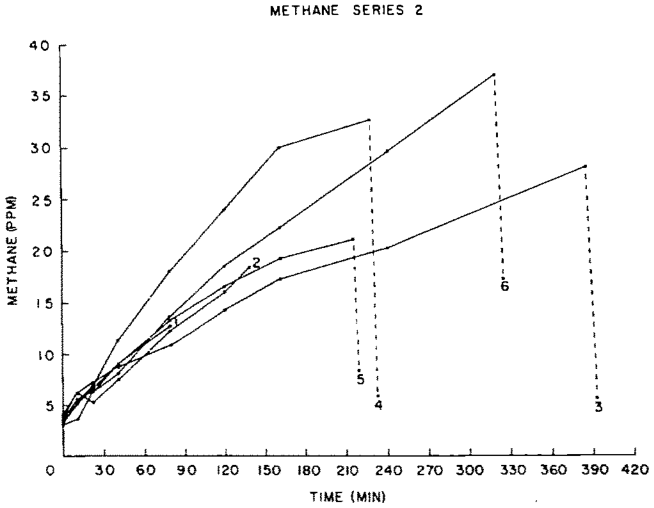

Figure 3. Using a high-flow semi-closed system for 33 min prior to circuit closure (Series II), the average methane concentration increased from 3.7 to 19.2 ppm after 120 min of closed-circuit anesthesia. Flushing the circuit with fresh anesthetic gases at high flows rapidly washed out the methane (dotted lines).

taminate the fresh gas inflow, or leach from materials in the anesthetic apparatus may appear in the circuit during closed-circuit anesthesia. In the present study we have observed the accumulation of nitrogen, methane, and acetone in the inspired gas during closed-circuit anesthesia. The concentrations of these gases reached appreciable levels during prolonged anesthesia.

We confirmed the finding of Barton and Nunn (2) that nitrogen accumulated in the closed circuit with time. Increasing the denitrogenation time from 8 to 33 min lessened the rate at which the concentration of nitrogen increased, as well as the final value of nitrogen observed, but significant levels were still achieved. With a short period of denitrogenation, nitrogen is probably transported to the lungs from all body tissue compartments. After 30 min of denitrogenation, a lean 70-kg subject still has 650 ml of nitrogen stored in body fat (5). The more obese the patient, the greater the nitrogen fat store available for transport to the lung. In addition, inflow gases may contain trace amounts of nitrogen. Current USP standards do not specify the maximum amount of nitrogen that may be present in medical grade oxygen, but what 9685 ppm of USP oxygen can consist of is not defined by USP standards (6). USP oxygen usually contains 3000–5000 ppm argon and 50 ppm methane. A spot check of our hospital liquid oxygen source showed 1900 ppm of nitrogen. If approximately 30 L of nitrous oxide are taken up and oxygen uptake is 300 ml/min, a 2-hr anesthetic in a patient with a combined circuit gas and functional residual capacity volume of 8 L would result in a 0.8% increase in circuit nitrogen. This compares with an observed value of 4.1% in our patients with long denitrogenation times. This difference between the nitrogen concentration in a closed circuit observed in the present study and that obtained by hypothetical calculations may be explained as follows. Before denitrogenation, body tissues of patients breathing ambient air are equilibrated with the nitrogen concentration in ambient air (79%). Upon breathing 100% oxygen, nitrogen stored in vessel-rich tissues (heart, brain, kidney, liver, etc.) is eliminated rapidly. In contrast, nitrogen stored in muscle, fat, and vessel poor tissues (cartilage, bone, etc.) is still being eliminated in exhaled air even after 30 min of breathing oxygen, with resulting accumulation in a closed circuit. In addition, it is often difficult to get a perfectly leak-tight anesthesia circuit in daily clinical practice, so that a small amount of ambient air may leak into a closed circuit and thus contribute to the increase in nitrogen concentration in a closed circuit. During the same time the concentration of argon in a closed circuit in our hypothetical patient would increase up to 2.3% after 2 hr if USP oxygen contains 5000 ppm argon. In a closed circuit, water vapor is usually saturated, and it must be subtracted when we calculate nitrous oxide concentration in a closed circuit. If the temperature of the gas in a circuit is 37°C, then the tension of water vapor in a circuit would be 47 mm Hg, the same as the tension of alveolar water vapor in the normal, unanesthetized patient. The folly of assuming that the tension of nitrous oxide can be calculated as 100 minus

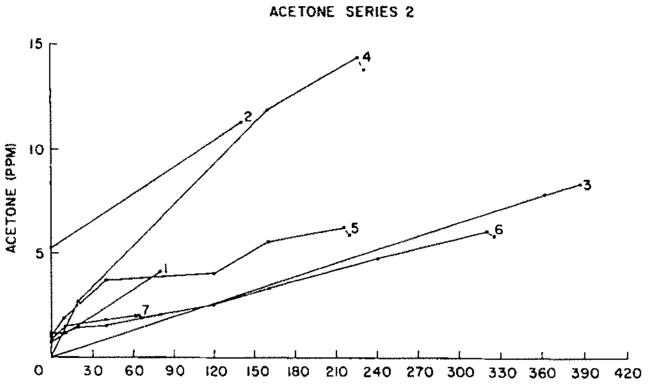

Figure 4. In Series II, the average acetone concentration increased from 1.3 ppm at the time the circuit was closed to 5.9 ppm at the end of the anesthesia. In contrast with nitrogen and methane, only a slight decrease in circuit acetone concentration followed flushing with fresh gases (dotted lines).

the percent oxygen is obvious. Occasional flushing at high flows with fresh gases provides a known concentration of nitrous oxide in the circuit and helps to avoid patient awareness during anesthesia. Flushing is highly effective in removing nitrogen (Fig. 2) largely because of low water:gas partition coefficient of nitrogen (0.015) (7).

Methane is present in the atmosphere both as a geophysical constituent as well as a pollutant. Usual urban levels are 1.2 ppm (8). Hence our observed methane accumulation may be due both to inflow contamination and redistribution of bowel gas by the blood to the lungs. As mentioned above, USP oxygen has been found to have up to 50 ppm methane (5). A spot check of our hospital liquid oxygen source showed 5.4 ppm of methane. A similar check of our nitrous oxide bank showed 2.5 ppm of methane. If the same hypothetical calculations are made with methane as were done with oxygen, over a 2-hr anesthetic the circuit methane concentration could increase to 24 ppm. This compares with 22 ppm in Series I and 17.9 ppm in Series II. The single patient in whom the concentration of methane in the circuit increased to 229 ppm at 72 min probably produced methane in his bowel. Bowel methane production is highly variable among patients because of differences in bowel flora, but can be as high as 100 ppm in the expired gas of healthy volunteers (9). If the same production rate was seen in our hypothetical subject with an expired minute volume of 5 L/min breathing USP oxygen with 50 ppm methane, 14 hr of closed-circuit anesthesia would be required to reach a flammable level of 5.4% methane in oxygen (10) within the circuit. Methane is also rapidly removed from the circle gas by flushing (Fig. 3) because of its low aqueous, lipid, and presumably, rubber partition coefficients (7). Hydrogen, a more common metabolite of bowel bacteria, can be excreted from the lungs at rates as high as 0.6 ml/min (11) and may represent a similar hazard. Maximal exhalation of hydrogen in a subject breathing with a combined circuit and functional residual capacity of 8 L could result in a flammable hydrogen–oxygen level of 4.6% (10) after 11 hr of closed-circuit anesthesia.

Acetone is normally produced in the liver during the metabolism of free fatty acids (12) and is excreted partially by the lungs (13). In diabetes and during fasting an elevated pulmonary excretion occurs (13). Because the water:gas and oil:gas partition coefficients of acetone are approximately 300 (14) and 42 (15), respectively, both water in tissues and water trapped within the circuit tend to dissolve the metabolically generated acetone and decrease its rate of increase in the gas phase. Important sources of water in our closed circuit include the prime in the humidifier, condensate in the tubing, and the products of the reaction of carbon dioxide with the absorbant. Consequently, flushing the circuit with fresh gas for 2 min fails to decrease the acetone concentration. Ethanol has a water–gas partition coefficient of 1200 (16) and may have similar accumulation and flushing kinetics to acetone. In closed-circuit anesthesia in the acutely intoxicated emergency patient, normal exhalation of ethanol will be prevented. Fresh gas flushing probably will be ineffective.

With the introduction of the precolumn cold trap for concentrating gas samples, more than 110 organic and inorganic compounds in the ppm to ppt range have been identified by gas chromatography–mass spectroscopy in human exhaled air during open circuit breathing (17,18). More than 32 of these compounds were present in the "zero grade air" that the subjects were inhaling (18). Recently the terpene lipid peroxidation product, isobutane, was detected after halothane anesthesia in humans (19). It seems reasonable that with the additional concentrating ability of closed-circuit breathing other compounds await identification. Closed-circuit anesthetic techniques may require far more stringent inspired gas standards (20).

We conclude that minor metabolic gases such as methane, acetone, and hydrogen and the common intoxicant ethanol can accumulate in the inspired gas during closed-circuit anesthesia. In extreme cases the uncommon combination of prolonged anesthetics, proper bowel flora, and substrate intake or alcohol consumption may result in a situation in which gases within the circuit may reach flammable levels. Nitrogen dissolved in body fat stores as well as nitrogen;

argon in the fresh gas inflow also may accumulate within the circuit, dilute the nitrous oxide, and may contribute to patient awareness, although awareness under anesthesia is not solely dependent on the nitrous oxide tension. Occasional flushing with fresh anesthetic gases is highly effective in reducing the concentrations of water-insoluble gases such as nitrogen, methane, and hydrogen. Highly soluble compounds such as acetone and presumably ethanol are, however, not readily removed by flushing. Dietary history, obesity, the purity of inflow gases, and the need for frequent flushing with fresh anesthetic gases should be considered when a closed-circuit technique is used.

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Review Article

Protamine: A Review of its Toxicity

Jan Charles Horrow, MD

Protamine is a polycationic peptide obtained from fish that is used to reverse anticoagulation induced by heparin. Between 1970 and 1979, approximately thirteen publications addressed the adverse cardiovascular effects of protamine. The last four years have produced an additional 30 reports. One of the primary explanations for this recent increase in the frequency of reports of adverse responses is the more widespread use of protamine owing to increased numbers of vascular and cardiovascular procedures.

Animal investigations in the early 1970s implied that protamine induced hypotension via a direct cardiac depressant effect. Recent advances in cardiovascular physiology and further investigations of the actions of protamine imply that this drug's effects are more complex. The purpose of this review is to examine the data available regarding the predictable and the idiosyncratic adverse cardiovascular responses to protamine. It is hoped that scrutiny of the animal investigations, prospective human studies, and case reports available in the literature will promote an understanding of the difficulties associated with use of this drug.

History and Pharmacology of Protamine

Friedrick Miescher began investigations of the cell nucleus in 1868 that led to the identification of a nitrogenous base bound to nuclear material of Rhine salmon sperm heads. He named this substance protamine (1). Subsequent studies by Kossel of various histones and protamines identified these compounds as proteins. Among proteins studied at that time, protamines possessed the simplest amino-acid compositions. Using protamines as prototypes, Meischer and his colleagues established the fundamentals of protein chemistry.

The protamines were named according to their sources—clupeine from herring, salmine from salmon, and scombrine from mackerel. Commercially available protamine is currently prepared from salmon milt, the secretion-laden male gonads. The ground and filtered milt is heated with alcohol (defatted), precipitated with alcohol and sodium chloride, then heated, filtered, and depyrogenated. The dried powder, prepared in Japan, is packaged and marketed in the United States as either powder (Upjohn Company, Kalamazoo, MI) or solution (Eli Lilly and Company, Indianapolis, IN).

Nearly 67% of the amino-acid composition of protamine is arginine, making it a highly alkaline polycationic compound with a molecular weight of about 4500 daltons (1). The multiple positive charges on protamine associate with negatively charged phosphate groups on DNA to form the nucleoprotamine of sperm (see Fig. 1). Heparin, a polyanionic mucopolysaccharide, induces anticoagulation by activating antithrombin III (2). When protamine is added to heparin in vitro, ionic forces form a stable precipitate (2,3). In fact, protamine has two active sites, one of which neutralizes heparin. The other exerts a mild anticoagulant effect (4). In the mid 1930s, Best encouraged his colleague Jaques to investigate protamine as an antidote to heparin in a clinical setting. Jaques was the first to develop the protamine titration assay for heparin and document in vivo neutralization of heparin using protamine (3).

Protamine has found clinical uses other than reversal of heparin-induced anticoagulation. Hagedorn et al. demonstrated its use to prolong absorption of subcutaneously administered insulin. Complexes of protamine and insulin include protamine–zinc insulin, with onset of action 7 hr after injection and 36-hr duration, and isophane insulin, with onset in 2 hr

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Address correspondence to Dr. Horrow, Department of Anesthesia, Hahnemann University, Broad and Vine Streets, Philadelphia, PA 19102.

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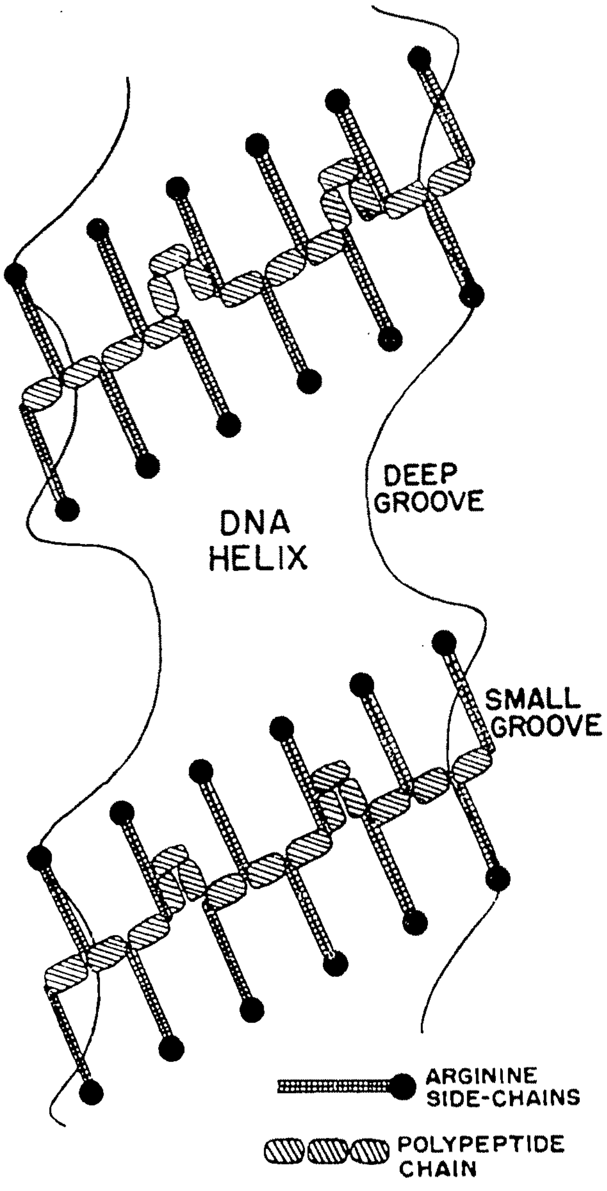

Figure 1. Wavy lines travelling vertically denote the DNA helix, with deep and small grooves identified. The linear sausage-shaped structure is protamine, with arginine side chains shown interacting with the phosphate groups of DNA (shown as black circles). (Reproduced with permission from Wilkins MHF. Physical studies of the molecular structure of deoxyribose nucleic acid and nucleoprotein. Cold Spring Harbor Symp Quant Biol 1956;21:83.)

and 24-hr duration (5). Isophane insulin is also known as NPH insulin (N for neutral, P for protamine, and H for Hagedorn).

Additional uses for protamine have been of transient popularity. Prior to the use of cardioplegia, some surgeons found that topical application of protamine upon the fibrillating heart decreased the amplitude of fibrillation (6). The drug was even seriously tried as an antineoplastic agent. Although those trials were unimpressive (7), more recent investigations demonstrate that protamine inhibits angiogenesis (8). Nevertheless, reversal of heparin-induced anticoagulation and prolongation of the effects of insulin remain the only clinical uses at this time.

Alternatives to protamine for reversal of heparin-induced anticoagulation include hexadimethrine and toluidine blue (9). Hexadimethrine is clinically effective as a heparin antidote (10), and has been used successfully when protamine was contraindicated (11). It is not currently available for clinical use in the United States. Toluidine blue is less suitable as a substitute for protamine because it is less efficacious and causes methemoglobin formation.

Prospective Studies

Adverse responses to protamine sulfate involve undesirable cardiovascular changes, particularly systemic hypotension. Laboratory and prospective clinical studies of the hemodynamic sequelae of protamine administration afford an unbiased view of the drug's predictable effects. These will be considered prior to an examination of published case reports of idiosyncratic responses.

Animal Investigations

Reports of protamine toxicity in animals appeared as early as 1900 (12). Beginning in 1939, toxic effects of protamine were reported in several species, including rabbits, rats, guinea pigs, mice, and dogs. Jaques (12) discovered marked variations in drug toxicity among species; dogs, for example, suffer transient and profound hypotension after receiving protamine, although this response occurs in rabbits, rats, guinea pigs, and mice only with unusually large doses. The canine preparation became a model for the study of protamine toxicity. The results of animal studies, summarized in Table 1, will be considered according to the hemodynamic variable studied.

Systemic circulation. A decrease in systemic blood pressure (SBP), first noted in 1900, occurs after rapid administration of protamine to dogs. Jaques (12) demonstrated hypotension to 30 mm Hg occurring 30 sec after the injection of 5–10 mg/kg of protamine. A "refractory" period of 4–6 hr occurred, during which a second dose of drug failed to elicit the hypotensive response. The rate of injection was important: infusion over 4 min was benign, but the same dose over 15 sec decreased SBP.

Table 1. Laboratory Investigations of Effects of Protamine in Dogs

Authors	Findings	Conclusions
Jaques (12)	Marked species variation in drug toxicity Need platelets for hypotensive response Rapid injection required for adverse response	Anaphylactoid response
Goldman et al. (13)	Decreased LVP, *dp/dt*, CO Elevated PAP, central and portal venous pressures	Negative inotrope[a]
Gourin et al. (17,18)	Increased *dp/dt* with constant left ventricular volume	Positive inotrope[a] Loss of preload
Radegran et al. (14,19,23)	Elevated PAP, pulmonary venous wedge pressure	Releases vasoactive substance
Fadali et al. (15)	Decreased *dp/dt*	Negative inotrope[a]
Marin-Neto et al. (16)	Decreased *dp/dt*	Negative inotrope[a]
Iwatsuki et al. (25)	Decreased rate of force development (isolated strips)	Negative inotrope[a]
Greene et al. (20)	No effect on fiber shortening or *dp/dt*	Not a negative inotrope; decreases SVR

[a] See text for discussion of the limitations of conclusions regarding inotropic state.

Goldman et al. (13) studied 74 dogs, 39 of whom had separate evaluations of the systemic and pulmonary circulations. SBP decreased after injection of protamine. This effect occurred whether protamine was injected intraarterially or intravenously and whether it was given into the systemic or the central circuit in dogs studied with a divided circulation. Also noted was an increase in portal venous pressure. Radegran et al. (14) administered 10 mg/kg of protamine to dogs at a rate of 30 mg/min. Systemic hypotension occurred 2.5–7 min after the infusion commenced. Repeat doses of protamine resulted in little or no hemodynamic change. Fadali et al. (15) gave heparin and protamine in rapid sequence to dogs, after which SBP decreased. Eight dogs investigated by Marin-Neto and colleagues (16) responded to 3 mg/kg of protamine infused over 2 min with decreased SBP.

Gourin et al. (17) prevented the decrease in SBP by rapidly administering fluid after giving protamine. They had observed marked splanchnic engorgement, suggesting that protamine altered venous capacitance. Measurements of systemic vascular resistance (SVR) disclosed a decrease of 20–33% (17,18). Decreased SVR was confirmed by Radegran and McAshlan (19) in a study of 21 dogs. However, Marin-Neto et al. (16) reported a 42% increase in SVR after administration of 3 mg/kg of protamine, and no change in SVR after 6 mg/kg. Those authors used an aortic clamp during initial measurements and released it 5 min after protamine administration. The sudden drop in SBP at a time when the effects of protamine were dissipating might have caused the increased SVR via the carotid sinus reflex.

These and other studies (20,21) demonstrate decreases in SBP after protamine injection. SVR also decreases in the absence of other interventions (18,19), but may be affected by reflex actions resulting from the decrease in SBP (16,17). Decreases in venous return may contribute to the lowered SBP via effects on cardiac preload.

Pulmonary circulation. Elevations of mean pulmonary arterial blood pressure (PAP) associated with protamine administration have been reported in three separate studies (13,19,22). Twenty-one dogs (19) showed elevations of PAP, pulmonary vascular resistance (PVR), and airway resistance. Pulmonary petechiae were prominent. In the same study in dogs pretreated with acetylsalicylic acid, protamine caused smaller increases in PAP and PVR, and the pulmonary petechiae were absent. A subsequent study (23) sought to differentiate between active pulmonary vasoconstriction and passive obstruction from platelet aggregates as the etiology of the increased PVR. This was accomplished by simultaneously measuring PAP, left atrial pressure (LAP), and the occlusion pressure in a small pulmonary vein. Both pulmonary vein pressure and PAP increased, while LAP was unchanged. Assuming that passive obstruction by platelet aggregates should decrease pulmonary vein pressure, active vasoconstriction is more likely the mechanism responsible for the increased PVR. The increases in PAP and PVR are not restricted to dogs. Four groups of pigs (22) displayed similar responses. Thus the response of the pulmonary circulation to rapid injection of protamine is elevation of PAP and PVR. This is likely due to active vasoconstriction in the pulmonary circuit.

Heart. Multiple animal investigations document a decrease in cardiac output (CO) after protamine administration (13,15,16,19,21,22). Decreases in CO or cardiac index (CI) can result from changes in one or more of the following: heart rate, afterload, preload, and contractility. These determinants will be considered in turn.

Most studies controlled heart rate by pacing, thus allowing no conclusions as to the effect of changes in heart rate on CO. As previously mentioned, SVR decreases. To the extent that this reduces afterload of the heart, SVR reduction should increase CO, not decrease it. With respect to preload, Goldman (13) demonstrated that protamine elevates central venous and portal pressures. In contrast, LAP was unchanged in the study of Radegran et al. (23). The splanchnic engorgement observed by Gourin et al. (17) is consistent with a reduction in venous return and hence a decreased preload. Fluid infusion was required to maintain a constant left ventricular volume in their studies (17). Although no clear consensus is apparent from these independent measures of preload, measurement of filling volumes as in the study by Gourin et al. appears the most appropriate, and it is reasonable to conclude that protamine decreases preload.

Alteration of the contractile state of the heart has received the most attention in animal investigations. Interpretation of these data requires an appreciation of the difficulties associated with measurement of the inotropic state. Although a complete discussion of the physiologic aspects of inotropy is beyond the scope of this review, the limitations associated with certain methods warrant mention. Efforts to measure inotropy focus on the velocity of contraction for a contractile element (V_{CE}) using the Hill model of muscle (24). Derivation of an expression for V_{CE} yields (K) (dp/dt)/LVP where K is a constant, dp/dt is the rate of increase of LVP during systole, and LVP is left ventricular intracavitary pressure. The maximum instantaneous value of the expression during a cardiac cycle, termed the peak measured velocity (V_{PM}), is used. Measures of *dp/dt* not adjusted for changes in LVP as well as ratios of mean values of *dp/dt* and LVP are less desirable. To complicate matters more, cardiac muscle does not behave according to the Hill model (24). Fiber length, as well as contractility, affects V_{PM}. Studies of isolated cardiac muscles are not easily compared with those utilizing the intact heart because the latter lack isometric conditions and also because ventricular geometry itself changes at low pressures. With these limitations in mind, however, the data available from animal studies will be presented.

Initial efforts by Goldman et al. (13) to measure inotropy during protamine administration revealed decreased LVP and *dp/dt*. However, when heart rate and left ventricular volume were kept constant (18), LVP and *dp/dt* both increased. In these studies (13,18), LVP was apparently measured during systole. Fadali et al. (15) confirmed the finding of Goldman et al. that *dp/dt* was depressed when ventricular filling volume was not controlled. Marin-Neto et al. (16) also found depression of *dp/dt* associated with protamine, although the mean left ventricular filling pressure was not significantly changed. None of these results permits firm conclusions regarding alteration of cardiac contractility by protamine. Even the results of the last mentioned investigation cannot be used to calculate V_{PM} because the instantaneous ratios of *dp/dt* to LVP were not recorded.

Iwatsuki et al. (25) measured isometric force and maximum velocity of shortening in vitro in strips of right ventricular trabeculae at 30°C. Isometric force and the rate of force development were depressed by the addition of 12.5 mg/L of protamine to the bathing solution.

Greene et al. (20) administered intracoronary protamine and measured systolic LVP and *dp/dt* as global indices of ventricular function. Intact myocardial fiber length served as a regional index. No changes occurred in any parameter, either when the coronaries were kept patent or when ischemia was induced. The absence of changes in the rate of myocardial fiber shortening in the intact heart provides rather compelling evidence for the lack of a protamine effect on the contractile state of the heart.

Role of platelets. Jaques (12) first reported significant thrombocytopenia associated with protamine administration in 1949. It began just before the systemic hypotension and reached a nadir, only 10% of baseline, within 4 min. Leukopenia also occurred. When thrombocytopenia was experimentally induced by glycogen, subsequent protamine administration did not decrease SBP, suggesting that platelets are required for this hypotensive response. Radegran et al. (14,19) found that protamine-induced thrombocytopenia was associated with elevation of PAP and depression of SBP. Acetylsalicylic acid did not prevent a 93% decrease in platelet count (19), although PAP and PVR alterations were blunted and pulmonary petechiae were prevented. The precise manner in which platelets participate in adverse responses to protamine is unknown.

Roles of heparin and thrombin. Many investigations compared the cardiovascular effects of protamine administered in the presence of circulating heparin and in its absence. In the study by Goldman et al. (13), decreases in LVP, *dp/dt*, and CO occurred in either instance. However, administration of heparin followed by protamine reduced SBP, while administration of protamine alone elevated SBP. In contrast, prior heparin did not alter the changes in SBP, PAP, and platelet count associated with protamine in the study by Radegran et al. (14). However, a curious "recharging" effect was discovered. The sequence: heparin → protamine → hemodynamic reaction → recovery → protamine was associated with no hemodynamic changes after the second protamine dose (14), corroborating the results of Jaques (12). But the sequence: heparin → protamine → hemodynamic reaction → recovery → *heparin* → protamine did result in typical hematologic and hemodynamic changes after the second protamine dose. A recent investigation in pigs (22), which revealed elevation of PAP and PVR and a decrease in CO after rapid administration of 3 mg/kg of protamine to heparinized animals, described no such changes when protamine was given before the heparin. The adverse hemodynamic effects did occur when protamine and heparin were mixed in vitro immediately before injection.

There is no ready explanation for the modulating effect of heparin on the responses to protamine. One possibility is that changes resulting from rapid injection of protamine are related to in vivo formation of a heparin–protamine complex (22). Although the recharging effect (14) is consistent with this hypothesis, hemodynamic effects occurring in the absence of prior heparin (14) remain unexplained. Several phenomena may be involved in these responses.

Radegran et al. (14) found that thrombin acted like heparin as regards recharging for an adverse response: even after multiple protamine infusions had extinguished hemodynamic changes, a hypotensive response could be obtained when protamine was infused after thrombin administration. In a subsequent study (23) Radegran et al. showed that thrombin, like protamine, increases PAP and pulmonary venous pressure, but that these changes occur immediately with thrombin infusion in contrast to a delay of several minutes with protamine infusion. Administration of reptilase, a fibrinogen depletor, did not modify the effects of protamine administration (14). A discussion of the systemic and pulmonary vascular effects of thrombin alone exceeds the limitations of this review (26). The interaction between the coagulation system and the cardiovascular response to protamine remains unclear.

Vasoactive mediators. There are few animal data but much speculation regarding the role of vasoactive mediators in protamine reactions. Jaques (12) documented unchanged blood histamine levels after protamine, but the assay used was insensitive. His data do not exclude a role for histamine. Radegran and McAshlan (19) were unable to modify the hemodynamic or hematologic effects of protamine with vagotomy. Administration of methysergide (19), a serotonin antagonist, was also unsuccessful; in fact, the systemic hypotension was worsened. New and sensitive assays for several vasoactive substances will expand these limited data.

Summary of animal investigations. Protamine decreases SBP and SVR and increases PAP and PVR. A decrease in CO is due at least in part to decreased preload. Protamine most likely has no effect on the contractile state of the heart. The cardiovascular changes are accompanied by decreases in platelet count, although the roles of circulating heparin, platelets, and vasoactive mediators are yet unknown.

Human Investigations

Prospective human studies on the cardiovascular effects of protamine vary in their methods with respect to the dose of protamine, rate of injection, route of administration, physical status of the patients, anesthetic conditions, the cardiovascular responses measured, and the times at which these responses were measured. Table 2 summarizes the conditions and results of ten prospective human studies. It is divided into two groups based upon the rate of drug administration.

Slow injection. The first group in Table 2 received protamine over three or more minutes. Jastrzebski et al. (27) studied 15 patients, 12 during valve replacement, and one each during closure of an atrial septal defect, complete repair of tetralogy of Fallot, and coronary artery vein grafts. All patients with valvular heart disease had at least one regurgitant valve. Mean PAP was unchanged from baseline levels 5 min after injection of protamine. PAP measured 15 min after drug administration, however, was elevated (35 mm Hg compared to a 26 mm Hg baseline). It seems unlikely that this increase was an effect of protamine because it occurred rather late. In addition, filling pressures of the heart, which could influence PAP, were not measured. SBP decreased transiently in most patients with protamine injection, but had returned to preinjection levels before the first hemodynamic measurements were made at 5 min; thus SBP is recorded as unchanged.

Ching and Leong (28) found a 24% elevation of CI 5 min after administering protamine slowly. Measurements made 15 min after protamine showed CI unchanged from baseline levels. SBP did not change

Table 2. Prospective Human Studies of Cardiovascular Effects of Protamine

Author	N	Dose of protamine	Rate of administration	SBP	SVR	PAP	PVR	RAP	LAP	CO/CI	Time(s) of measurement[a]	Other comments
Slow injection												
Jastrzebski et al. (27)	15	6 mg/kg	5 min			↑				0	5 and 15	
Ching and Leong (28)	10	By ACT[b]	5 min	0	0		0			↑	5 and 15	
Conahan et al. (29)	15	3 mg/kg	5 min	0				0		0	1 and 5	
Sethna et al. (30)	9	2.5 mg/kg	4 ± 1 min	0	0	0			0	0	10	Good LV[e]
Sethna et al. (31)	11	214 ± 47 mg	5.5 ± 2 min	0	0				0	↓	10	Poor LV[e]
Michaels and Barash (32)	25	1.3 mg/mg[c]	0.5 or 1 mg·kg^{-1}·min^{-1}	0	0	0	0	0	0	0	5	Good LV[e]
Michaels and Barash (32)	15	1.3 mg/mg[c]	0.5 or 1 mg·kg^{-1}·min^{-1}	0	0	0	0	0	0	0	5	Poor LV[e]
Hanowell et al. (33)	16	1.5 mg/mg[c]	5 min	0		0		0	0	0	5	Good LV[e]
Rapid injection												
Ching and Leong (28)	10	By ACT[b]	<0.5 min	0	0		0		↓	0	5 and 15	
Shapira et al. (34)	8	150 mg/m^2	0.5 min	↓	↓		↓		↓	↑	every 30 sec	V_{PM} ↓[f]
Shapira et al. (34)	14	150 mg/m^2	1 min	↓	↓		↓			↑	every 30 sec	V_{PM} ↓[f]
Pauca et al. (35)	79	1.3 mg/mg[c]	1–3 min	↑	0		0	0[d]	0[d]	↑	5 and 7	Via aorta[g]
Frater et al. (36,37)	8	400–500 mg	1.5 min	↓	↓					↑	2	Via RA[g]
Frater et al. (36,37)	9	400–500 mg	1.5 min	0	0					0	2	Via LA[g]
Milne et al. (38)	5	3 mg/kg	0.5 min	↓	0	0	0	0	0	0	1,2.5,5,10	Via aorta[g]
Milne et al. (38)	5	3 mg/kg	0.5 min	0	0	0	0	0	0	0	1,2.5,5,10	

Abbreviations used: N, number of patients; SBP, systemic blood pressure; SVR, systemic vascular resistance; PAP, pulmonary artery pressure; PV pulmonary vascular resistance; RAP, right atrial or central venous pressure; LAP, left atrial or pulmonary capillary wedge pressure; CO/CI, cardiac outp or cardiac index; ↑ increased; ↓ decreased; 0, no change.

[a] Minutes after start of infusion.

[b] Protamine dose determined by activated clotting time according to method of Bull (68).

[c] Dose measured in mg of protamine per mg of remaining heparin as determined by protamine titration.

[d] Volume was infused during drug administration.

[e] Good LV is good left ventricular function; Poor LV is poor left ventricular function.

[f] V_{PM} is maximum value of instantaneously calculated *dp/dt/P* (see text for discussion).

[g] Protamine was administered by peripheral or central venous cannula except as noted via right atrium (RA), left atrium (LA), or aortic root (aorta).

with the slow injection of protamine and decreased only transiently and slightly (10–15%) after the rapid injection of protamine.

Fifteen patients studied by Conahan et al. (29) had stable SBP, CO, and central venous pressure during slow injection of protamine. In their study, responses to protamine prepared freshly from powder were similar to those observed after injection of prepackaged protamine solution. One patient had an anaphylactoid response to protamine. Neither ionized nor total plasma concentrations of calcium changed during protamine administration.

In addition to measuring SBP, PAP, pulmonary capillary wedge pressure, and CI, Sethna et al. (30) determined coronary sinus blood flow and lactate concentrations before and after injecting protamine. In nine patients with good left ventricular function, no significant hemodynamic alterations occurred. Coronary vascular resistance increased by 26%, a finding the authors attributed to decreased myocardial oxygen extraction. In a subsequent letter (31), the authors reported a similar study of eleven patients with poor left ventricular function. Cardiac index decreased by 13% ($P < 0.01$). The authors conclude that the response to protamine may depend upon th degree of recent circulatory stability.

When Michaels and Barash (32) measured hemodynamic changes after protamine in patients with goo or poor left ventricular function, no hemodynami parameter measured 5 min after completion of th infusion was significantly changed. In patients wit poor left ventricular function, SBP and SVR decrease 15 min after start of the infusion. In contrast to th study by Sethna et al. (31), CI in patients with poo left ventricular function was not depressed.

Hanowell et al. (33) measured the effects of protamine on SBP, PAP, right atrial pressure, heart rate pulmonary capillary wedge pressure, and CI in 1 patients with good left ventricular function. No change occurred 5 min after a 5-min infusion of protamine.

To summarize the effects of slow injection (>3 min of protamine as determined in these investigations SBP decreased minimally if at all; CI remained unchanged, although there were varying results in stud ies of patients with poor ventricular function; and PAP also remained unaffected.

Rapid injection. Five studies utilized rapid infusion of protamine (within 3 min). Shapira et al. (34) measured cardiac output by an electromagnetic flow probe, and calculated (*dp/dt*)/LVP as an index of ventricular contractile state. When administered over 30 or 60 sec, protamine lowered SBP, SVR, PVR, and LAP. Cardiac index increased. The maximum value of instantaneously calculated (*dp/dt*)/LVP, the V_{PM}, decreased slightly (less than 12%) with protamine injection. This small but significant decrease in V_{PM} permits little to be concluded about a change in contractile state because of the limitations of the Hill model upon which V_{PM} is based.

Pauca et al. (35) administered protamine into the ascending aorta. Rapid volume infusion was required to maintain filling pressures. Under these conditions, CO increased and SBP increased, the latter by only 2 mm Hg. The authors concluded that volume infusion provided hemodynamic stability and that aortic administration of protamine was of no particular advantage.

Right and left atrial injection sites of protamine were compared by Frater et al. (36). Hemodynamics were unchanged with left-sided injection. Decreases in SBP and SVR and increases in CI occurred, however, with right-sided injections. However, at least one of the eight patients in the latter group experienced an anaphylactoid reaction (37). This patient's data were not excluded from the analysis and may have confounded the comparison of effects of right vs left intracardiac injection on SBP and SVR. Thus the authors demonstrated neither the superiority of left-sided injection to right-sided injection, nor, because of the small sample size of the study, any protective effect of left-sided injection against development of an anaphylactoid reaction. Frater et al. (36) measured plasma histamine 3 min after the rapid injection of protamine. A small but statistically significant elevation occurred after injection into the right side of the heart, leading the authors to postulate that histamine release in the pulmonary circulation contributes to the hemodynamic effects of rapid protamine injection.

Milne et al. (38) measured SBP, SVR, PAP, PVR, LAP, CI, and central venous pressure after protamine injected intravenously in a group of patients and intraaortically in another group. No hemodynamic variable was changed in either group with the exception of a 20% decrease in SBP 1 min after intraaortic injection that resolved within another 1.5 min.

The above five studies (28,34–36,38) of rapid injection of protamine in patients document decreased SBP and SVR (34,37). Cardiac index increased, whether by a reflex mechanism or by some direct effect (34–36). There is no evidence for elevations in PAP (38) or PVR (28,34,35). Filling pressures of the heart probably decrease (34,35). There is scant evidence for direct myocardial depressant effect of protamine (34), and, because the Hill model has questionable application to intact cardiac muscle, it is difficult to interpret a slightly decreased V_{PM} as evidence for myocardial depression.

Summary. The prospective human studies considered above reveal that in some patients protamine is associated with decreases in SBP and SVR, especially when administered rapidly. Cardiac output increases reflexly, except perhaps in patients with less compliant ventricles, which are more dependent on preload to maintain stroke volume. In the latter, decreases in filling volume associated with protamine can lower CO. Regardless of the rate of administration, protamine does not produce predictable, acute increases in PAP, although increases in PAP may occur during idiosyncratic reactions (see the section on idiosyncratic reactions below). Left atrial or aortic administration of protamine may not confer protection from its hemodynamic or idiosyncratic sequelae (see below). Little evidence exists to conclude that protamine directly depresses contractility of the human heart.

Idiosyncratic Reactions

Antigenicity

Protamine is a nonhuman protein, the prototypical class of compounds that trigger antibody production by the immune system. Despite this, protamine has been reported to be minimally antigenic (39). Recent reports of positive skin tests to protamine demonstrate that the drug can, however, initiate an immune response (11). In addition, antibodies to protamine have been measured in several patients (40–42).

Immunologic studies of men who have undergone vasectomy provide perspective on the issue of protamine antigenicity (42). The testes are an immunologically privileged organ. Beginning at puberty, a "blood–testes" barrier sequesters developing sperm cells from the rest of the body, preventing the immune system from attacking the immunologically foreign sperm. With occlusion of ejaculatory paths at vasectomy, sperm are absorbed systemically. This stimulates antibody production, so that one year after vasectomy, 73% of men harbor sperm-agglutinating antibodies (43) and 22% of men have autoantibody to human protamines (44). Human protamines correspond closely to salmon protamine (42). Autoantibodies to human protamine may thus cross-react with commercially prepared protamine. Nevertheless, no case report of an anaphylactoid response to protamine in patients with prior vasectomies has been reported.

Adverse Response with Prior Exposure

Antiprotamine antibody production may be stimulated by exposure to protamine or to a similar antigen. Prior exposure to protamine is often obvious. Protamine may be administered after many procedures requiring heparin for anticoagulation, including vascular surgery, cardiac catheterization, cardiopulmonary bypass, hemodialysis, and blood component donation (pheresis).

Injection of protamine-containing forms of insulin is a less apparent means of achieving prior exposure. Both protamine–zinc insulin and NPH insulin contain protamine, which is used to delay absorption of insulin upon subcutaneous injection (5). Some diabetic patients receiving these insulin preparations develop sensitivity to subcutaneous injections. Kern et al. (39) reported 104 patients with skin reactivity to protamine–zinc insulin. No patient displayed a cutaneous reaction to protamine alone, implying that insulin itself or the protamine insulin complex was the sensitizing agent. In contrast, Sanchez et al. (45) described a patient with cutaneous reactions to NPH insulin and to protamine. Hyposensitization injections with protamine alone in increasing dosages ablated the cutaneous response, thus allowing the patient to receive subsequent NPH insulin without difficulty.

Most patients do not develop cutaneous responses to protamine-containing insulins. These patients may, nevertheless, react systemically to intravenous protamine. Moorthy et al. (46) described a typical anaphylactoid response during vascular surgery in a diabetic patient treated with protamine–zinc insulin. However, the only datum to support participation of the immune system in that patient's response was elevation of IgE levels measured one month after the event. This isolated finding is rather nonspecific.

Table 3 lists case reports of idiosyncratic reactions to protamine. Doolan et al. (11) reported a patient taking protamine–zinc insulin who developed an anaphylactoid response after cardiopulmonary bypass. Cutaneous testing with protamine was strongly positive despite the absence of a history of sensitivity to protamine–zinc insulin. Of 11 patients taking NPH insulin with reported anaphylactoid reactions to protamine (47–50), only one of four patients studied by cutaneous testing (48) had clearly positive results. In fact, of all 13 patients reported to have suffered anaphylactoid reactions due to prior exposure to protamine-containing insulin preparations (11,46–50), only one case report (11) provides convincing evidence of an immune-mediated phenomenon. The other 12 cases lack sufficient documentation. Sensitization to protamine secondary to use of insulin preparations appears to be an uncommon but serious clinical entity that requires rigorous investigation to establish the diagnosis.

A single intravenous exposure to protamine is unlikely to stimulate antibody production. Consider the thousands of patients who receive protamine after cardiac catheterization and then are rechallenged at the conclusion of cardiopulmonary bypass. Of course, in many cases the intervening period is only days to weeks, a time too brief for antibodies to form. Holland et al. (49) reported two patients who developed delayed anaphylactoid responses 30 min after protamine injection at the conclusion of cardiopulmonary bypass. One patient had undergone catheterization 7 days, the other 19 days before surgery. Skin tests were negative in each patient. Why implicate protamine? Often the only evidence pointing to a drug as the provocative agent is a temporal relationship between drug administration and adverse response. When 30 min separate these events, this association becomes weak indeed.

In contradistinction, anaphylactoid responses of a patient to protamine given during cardiac catheterization 1.5 yr after cardiopulmonary bypass were reported by Doolan et al. (11). Positive results with cutaneous testing implicate protamine allergy in that patient. Best et al. (51) reported an anaphylactoid response in a patient given intravenous protamine on three prior occasions. Serial measurements of serum complement proteins and their split products demonstrated activation of the classical pathway during this response. Thus of the 7 case reports (11,41,49,51,52) of patients who sustained adverse responses to protamine and who had received intravenous protamine in the past, two reports (11) implicated an immune-mediated response, one demonstrated IgG antibody to protamine (41), and one documented complement consumption (51) during the response.

Adverse Response without Prior Exposure

Reports of anaphylactoid responses to protamine in patients with no history of prior exposure are of three types: patients allergic to fish; patients developing delayed capillary leak after cardiopulmonary bypass; and patients with catastrophic pulmonary vasoconstriction after cardiopulmonary bypass.

Cross-reacting antibodies caused an anaphylactoid

Table 3. Case Reports of Idiosyncratic Reactions to Protamine

Author	Prior exposure	Intervening period	Circumstances of rechallenge	Skin tests	Other data
Lakin et al. (41)	Pheresis	5 months	Pheresis	Positive	IgG to protamine
Moorthy et al. (46)	PZn insulin	—	Vasc surg	Not done	Elevated IgE
Andersen and Johnson (52)	Hemodialysis	various	Hemodialysis	Not done	High or low blood pressure
Cobb and Fung (47)	NPH insulin	—	Vasc surg	Not done	
Doolan et al. (11)	Vasc surg	6 weeks	Vasc surg	Positive	
Doolan et al. (11)	PZn insulin	—	CP bypass	Positive	
Doolan et al. (11)	CP bypass	1.5 yr	Cardiac cath	Positive	
Best et al. (51)	CP bypass	2 weeks	Cardiac cath	Not done	Complement-mediated
Vontz et al. (50)	NPH insulin	—	Vasc surg	Not done	
Grant et al. (48)	NPH insulin	—	CP bypass (7)[a] Vasc surg (1)	Not done (4) Positive (1) Negative (3)	8 patients reported
Holland et al. (49)	Cardiac cath	7 days	CP bypass	Negative	Delayed reaction
Holland et al. (49)	Cardiac cath	19 days	CP bypass	Negative	Delayed reaction
Holland et al. (49)	NPH insulin	—	CP bypass	Not done	Immediate reaction
Holland et al. (49)	Not reported		CP bypass	Not done	Delayed reaction
Jackson (26)	?Insulin		Vasc surg	Not done	Diabetic patient
Jackson (26)	Not reported		Vasc surg	Not done	
Caplan and Berkman (53)	Not reported		Pheresis	Not done	4 of 140 donors; 2 allergic to fish
Nordstrom et al. (69)	Not reported		CP bypass	Not done	Immediate
Olinger et al. (54)	Not reported		CP bypass	Not done	Delayed reactions in 4 patients
Knape et al. (40)	Not reported		CP bypass	Positive	Codfish allergy by RAST; elevated IgE
Lowenstein et al. (56)	Not reported		CP bypass (5) Cardiac cath (1)	Not done	Elevated pulmonary vascular pressure in 6 patients

Abbreviations used: Vasc surg, vascular surgery; PZn, Protamine zinc; CP, cardiopulmonary; Cath, catheterization; RAST, radioallergosorbent test.

[a] Numbers in parentheses denote number of patients.

reaction described by Knape et al. (40) in a patient who received protamine after cardiopulmonary bypass. This patient described prior episodes of syncope when eating true fish. In addition, cutaneous testing to protamine was strongly positive, IgE levels were elevated, and codfish allergy was documented by radioallergosorbent testing (RAST). Caplan (53) reported four pheresis donors who reacted to protamine, of whom two claimed allergy to fish. It should be noted that allergy to shellfish may be irrelevant. Shellfish and true fish are quite distinct phylogenetically. No reports of adverse response to protamine specifically mention shellfish allergy.

Noncardiac pulmonary edema and anasarca developing approximately 30 min after the administration of protamine have been reported in seven patients. Olinger et al. (54) described four patients with this syndrome after cardiopulmonary bypass. Holland et al. (49) have recently described another three patients, two of whom had received protamine during cardiac catheterization (see above). None of the seven patients had evidence of protamine allergy. Protamine has been implicated only by elimination of other possible factors, not by compelling evidence of true allergy to protamine. In fact, three additional cases reported by Culliford et al. (55) were ascribed to "an unknown type of allergic reaction to blood or blood products." Regardless of the causative agents, the syndrome of pulmonary edema and anasarca after protamine is totally unpredictable and often fatal; three of the seven patients cited above died. One such response at the author's institution (unpublished) resulted in visceral edema so profound as to prevent sternal closure.

Another adverse response to protamine, catastrophic pulmonary vasoconstriction, may occur without documented prior exposure to the drug. This reaction involves marked pulmonary vasoconstriction and systemic hypotension occurring immediately after injection of protamine. Lowenstein and colleagues (56) reported six such cases, five of whom had abnormal pulmonary hemodynamics preoperatively because of underlying valvular heart disease. This type of reaction resembles that documented in canine investigations (12–14,19,23) in which marked thrombocytopenia was found (12,14). This reviewer measured platelet counts immediately prior to and after a pulmonary hypertensive response in one patient: a dramatic decline to 16% of control occurred (unpublished). In contrast, Bjoraker and Ketcham (57) reported that platelet counts decreased only to 72% of control in 14 patients given protamine, but in none did an adverse response occur. Also, the pulmonary hypertension occasionally seen in patients after protamine is quite short-lived, similar to that seen in dogs. Immediate rechallenge with protamine was uneventful after recovery in the reviewer's patient, a feature consistent with the canine response.

Heterogeneity of Adverse Responses to Protamine

Types of Reactions

The preceding discussion demonstrates that adverse cardiovascular responses to protamine fall into three distinct types: transient hypotension related to rapid drug administration; anaphylactoid responses; and catastrophic pulmonary vasoconstriction (Table 4). The anaphylactoid responses may be subdivided into three groups: true anaphylaxis, immediate anaphylactoid reactions, and delayed anaphylactoid responses. True anaphylaxis is mediated by antibodies. Immediate anaphylactoid responses not involving antibodies are thought to be mediated via complement activation (58,59). Delayed anaphylactoid responses have been claimed in various reports (49,54); however, a strong link to protamine administration has never been demonstrated.

Table 4. Classification of Adverse Responses to Protamine

I. Hypotension related to rapid administration.
II. Anaphylactoid responses.
  A. Antibody-mediated anaphylaxis.
  B. Immediate anaphylactoid response without antibody involvement.
  C. Delayed anaphylactoid response (noncardiac pulmonary edema).
III. Catastrophic pulmonary vasoconstriction.

Table 5 summarizes the characteristics of idiosyncratic and nonidiosyncratic responses to protamine. Transient systemic hypotension associated with rapid administration of protamine (36,60) may be allowed to reverse spontaneously or may be treated with intravenous fluids, depending upon the magnitude of physiologic response and the patient's condition. Because other types of protamine response cannot be excluded initially and should receive more aggressive therapy, rapid injection of protamine is not recommended.

Anaphylactoid responses to protamine are characterized by edema of the skin, mucosa, and viscera, decreased SVR, bronchospasm, and occasionally flushing. In the delayed form (type IIC), these features may be quite insidious at onset. Treatment should include oxygen, intravenous fluids, positive pressure ventilation, and early aggressive use of epinephrine. Additional vasoactive drugs may be required to maintain systemic blood pressure. Antihistamines, aminophylline, and steroids are also employed in the treatment of anaphylactoid reactions (58). In most cases, definitive diagnosis will not be achieved. Skin testing, immunoglobulin electrophoresis, and RAST are among the many techniques available (58) to support a diagnosis of true anaphylaxis (type IIA). Serial serum levels of complement fragments may disclose a pattern consistent with a complement-mediated anaphylactoid reaction (type IIB). Prevention of anaphylactoid response to radiocontrast material in patients with a presumed or diagnosed previous adverse response has been documented for example, with a regimen utilizing antihistamines and steroids prior to reexposure (58,61). This reviewer recently cared for a patient who developed facial and throat tightening after protamine administration during cardiac catheterization. Steroid and antihistamine prophylaxis was utilized during cardiopulmonary bypass, and no adverse response to protamine occurred (unpublished observation). The diagnosis and prevention of delayed anaphylactoid reactions to protamine (type IIC) are unclear. These aspects can be addressed only after elucidation of the mechanism of this response and better definition of the association of protamine with this response.

Catastrophic pulmonary vasoconstriction (type III) is accompanied by right ventricular dilation, pulmonary arterial hypertension, decreased left ventricular filling pressure, and systemic hypotension. Diagnosis is facilitated by the presence of a pulmonary arterial catheter. This syndrome has occurred after minimal doses of protamine (10 mg) and may resolve spontaneously. Treatment with isoproterenol is reasonable; several patients have been treated successfully with epinephrine (56). There is as yet no evidence that extremely slow administration of protamine prevents this response.

Incidence of Reactions

Although there are no prospective studies to determine the incidence of idiosyncratic and nonidiosyn-

Table 5. Characteristics of the Various Adverse Responses to Protamine

Response type	I Rapid administration	IIA Anaphylaxis	IIB Immediate anaphylactoid	IIC Delayed anaphylactoid	III Pulmonary vasoconstriction
Distinguishing features	Transient $\downarrow$ SVR	$\downarrow$ SVR, flushing, edema, and bronchospasm		Massive edema, insidious onset	Dilated right heart, $\uparrow$ PAP, $\downarrow$ SBP
Treatment	Fluid or none	O_2, fluid, epinephrine, steroids, antihistamines, positive pressure ventilation			Isoproterenol or epinephrine
Diagnosis	By history	Skin tests, RAST, immunoglobin electrophoresis	Serial serum levels of complement fragments	?	PA catheter and time course
Prevention	Use slow injection	Antihistamine and steroid preparation		?	?Slow administration
Incidence	Common	Uncommon	Uncommon	?	Rare

cratic responses to protamine, some estimates may be obtained from published reports. Rapid administration results in systemic hypotension (type I response) in most patients. Coulon et al. (62) speculate that even a small dose of protamine sulfate will change SBP, and that the direction of change depends upon the degree of volume loading: in hypovolemic patients, SBP decreases; in hypervolemic patients, SBP increases in response to protamine. Although most clinicians who frequently administer protamine think that the response of blood pressure is variable even with slow administration of protamine, experimental verification of the speculations of Coulon et al. is lacking.

With regards to type II reactions, Caplan (53) reported that 4 of 140 pheresis donors (3%) developed responses attributed to protamine. Lakin et al. (41) in their report of anaphylaxis in pheresis donors, record 4 of 11 repeat donors with symptoms of a reaction to protamine. One of five people who donated a third time had an adverse response. Of 15 cardiac surgical patients studied prospectively by Conahan et al. (29), one developed an anaphylactoid response. Masone et al. (37) reported one of 17 patients with anaphylactoid reaction in their prospective study. Thus anaphylactoid reactions (type II) may occur more frequently than the idealized "rare event" rate of one per 20.

One of 40 patients studied by Michaels and Barash (32) sustained what may have been a pulmonary vasoconstrictive response (type III) to protamine. The report by Lowenstein et al. (56) describes an incidence of 3 per 100 for pulmonary vasoconstriction. Type III reactions occur rarely, but institutional rates are likely to vary with the characteristics of the patient population because type III reactions appear to be especially likely to occur in patients with abnormal pulmonary hemodynamics.

Further Research

In the decade 1970–1979, studies were conducted using the dog model, and there were few case reports of idiosyncratic reactions in patients. After the report by Moorthy et al. (46) in 1980, a large number of publications dealing with adverse responses to protamine appeared (11,47–50). In addition, renewed interest in the cardiovascular effects of protamine prompted several prospective human studies (29–32,34), including some that compared venous and arterial injections (36,38).

Future work will address the pathophysiology, epidemiology, and clinical aspects of adverse responses to protamine. In the realm of pathophysiology, further investigations using the animal models should seek to identify the vasoactive substance(s) responsible for the hemodynamic effects of protamine. In particular, histamine release needs to be restudied employing the more sensitive assays now available. Bradykinin, serotonin, and thromboxane are also likely candidates as mediators of hemodynamic changes. Identification of the vasoactive mediator(s) may proceed via clinical studies as well as those in animals.

Several factors suggest eicosanoid compounds (prostaglandins and related substances) and platelets play a role in the pulmonary vasoconstrictive reaction. First, thromboxane A_2, produced from arachidonic acid via the cyclooxygenase pathway, is a potent pulmonary vasoconstrictor and platelet aggregator (63). Produced in platelets and possibly endothelial cells, thromboxane A_2 has a half-life of 30 sec, which is consistent with the time course of the pulmonary vasoconstrictive response. Second, endotoxic shock has many features similar to the pulmonary vasoconstriction syndrome: transient pulmonary hypertension and systemic hypotension, thrombocytopenia, leukopenia, and subsequent increased capillary permeability. The pulmonary hypertension in endotoxic shock can be prevented by indomethacin; similarly, acetylsalicylic acid blunts the hemodynamic response to protamine in dogs.

Each of the patients reported by Lowenstein et al. (56) had altered pulmonary hemodynamics because of valvular heart disease or cardiogenic shock. Is there some alteration of the pulmonary vasculature that may predispose these patients to protamine-induced pulmonary hypertension? For example, abnormal vascular endothelium might be deficient in synthesis of prostacyclin, a potent vasodilator, thus allowing a protamine-induced release of thromboxane from platelets to cause net pulmonary vasoconstriction. It is intriguing to note that prostaglandins were first discovered in semen, and that marine animals produce a series of prostaglandins that have three double bonds in side chains, compared with two in the arachidonic acid series (63). Could the pulmonary vasoconstriction seen in some patients result from impaired endothelial cell prostacyclin synthesis coupled with an exogenous source of thromboxane-like material present as a contaminant in protamine preparations? This possibility should be seriously entertained, considering the source of protamine and the extraction process used to prepare the commercially available product.

Additional pathophysiologic issues related to all types of adverse protamine response include the role of complement proteins (64–66), the role of heparin–protamine complexes, and the manner by which thrombin acts like heparin in "recharging" the system. With respect to protamine's effects on cardiac contractility, new techniques utilizing pressure–volume diagrams of the left ventricle (67) may permit more appropriate measurement of the elusive entity termed contractility and how protamine affects it.

The second realm of investigation is epidemiologic. The incidence of adverse responses to protamine may be determined prospectively for the surgical population as a whole and for the various subgroups at risk, such as diabetic patients receiving protamine-containing insulins. Development of a RAST for protamine would permit safe and accurate identification of patients at risk for anaphylaxis. These advances would permit a more informed approach to what appears now to be an unacceptably high risk (>5%) of adverse responses to protamine. Regarding the delayed anaphylactoid response (type IIC), either the link with protamine needs to be made firm or the association abandoned.

Finally, in the clinical realm, consideration should be given to reintroducing hexadimethrine in the United States as a protamine substitute. Advances in the medical and surgical treatment of patients with occlusive vascular disease or valvular heart disease result in a growing population of surgical patients at risk for an adverse idiosyncratic response to protamine. It is reasonable to expect that an alternative drug to protamine will be available.

With increased attention to protamine toxicity and research, it is expected that many questions about the untoward actions of this drug will be resolved. This review aimed to provide perspective to guide these efforts.

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Technical Communication

Subjective Evaluation of Anesthesia Textbooks:
Relation to Currency

Edwin S. Munson, MD

An objective method for the evaluation of the currentness, or up-to-dateness, of biomedical textbooks has been described by Pittinger (1). The objectively derived currency scores have not been compared with subjective impressions of the usefulness or value of textbooks. This study was performed to evaluate the hypothesis that the subjective value of textbooks is related to textbook currency. Accordingly, we investigated the relation between the objective assessment of currency scores and the subjective evaluation of usefulness by a large population of anesthesia personnel.

Methods

Twelve anesthesia-related textbooks from a group of 64 that had been previously evaluated for currentness were selected for study (1,2). These texts are listed in Table 1. They were chosen because of the belief that they would be well-known to the evaluators and because they represent a wide variety of up-to-dateness, with currency scores that varied from 48 to 204.

A one-page questionnaire was mailed to the directors of 33 university anesthesia residency programs for distribution to their clinical anesthesia personnel. The teaching programs represent relatively large teaching programs over a wide geographic area. The instructions were the following: "Please indicate your estimate of usefulness or value of the following textbooks by circling the appropriate number; 1 = none, 2 = some, 3 = average, 4 = above average, 5 = most. Mark unfamiliar books NA (no answer). Designate your proper category: resident (year), nurse, or faculty." The strength of the correlation of the rankings between these subjective scores and the previously derived objective scores (1,2) was tested by using Spearman's rank correlation (3). Differences

Table 1. Anesthesia Textbooks Rated

1. Adriani J. The pharmacology of anesthetic drugs. 5th ed. Springfield, IL: Thomas, 1970.
2. Atkinson RS, Rushman GB, Lee JA. A synopsis of anaesthesia. 8th ed. Chicago: Year Book Medical Publishers, 1977.
3. Bromage PR. Epidural analgesia. 2nd ed. Philadelphia: Saunders, 1978.
4. Churchill-Davidson HC, ed. A practice of anaesthesia. 4th ed. Philadelphia: Saunders, 1978.
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Received from the Department of Anesthesiology of the University of Florida College of Medicine, and from the Anesthesiology Service, Veterans Administration Medical Center, Gainesville, Florida. Accepted for publication October 19, 1984.

Address correspondence to Dr. Munson, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, KY 40536.

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Table 2. Mean (± SEM) Questionnaire Scores, Currency Scores, and Rankings for Twelve Anesthesia Textbooks Shown in Table 1, Based on 692 Respondents from 29 Anesthesia Residency Programs

	Textbooks											
	1	2	3	4	5	6	7	8	9	10	11	12
n[a]	294	309	484	525	368	377	658	593	678	617	664	280
Questionnaire scores[b]												
PGY-2	257	244	349	275	244	310	362	381	365	394	449	338
	(6)	(8)	(39)	(40)	(16)	(19)	(96)	(66)	(95)	(71)	(98)	(24)
PGY-3	251	262	350	282	237	294	377	389	350	375	455	325
	(17)	(22)	(78)	(51)	(29)	(39)	(93)	(88)	(98)	(90)	(100)	(30)
PGY-4	311	275	309	264	250	286	379	400	385	413	458	329
	(23)	(20)	(83)	(70)	(35)	(55)	(98)	(98)	(100)	(95)	(95)	(35)
Nurses	315	287	321	341	330	284	355	365	411	387	432	347
	(73)	(56)	(48)	(84)	(77)	(39)	(89)	(67)	(99)	(85)	(88)	(46)
Faculty	201	276	367	320	202	313	387	399	402	373	432	316
	(58)	(65)	(81)	(95)	(70)	(75)	(97)	(94)	(99)	(95)	(96)	(49)
Mean	233	275	355	312	231	306	377	392	387	380	440	324
± SEM	6	6	4	4	6	5	4	4	4	4	3	6
Rank	11	10	6	8	12	9	5	2	3	4	1	7
Currency scores[c]	99	78	96	76	48	130	204	154	152	128	143	192
Rank	8	10	9	11	12	6	1	3	4	7	5	2

[a] Total number of respondents for each textbook. Note that the number of no answer (NA) responses for each textbook equals 692 minus (*n*). (%) Percentage of respondents that ranked each textbook. The percentage of no answer (NA) responses equals 100 minus (%).

[b] Questionnaire scores were multiplied by 100 to facilitate tabulation.

[c] Currency scores from data of Pittinger (1) and Munson and Pittinger (2).

between pairs of the Spearman correlations were evaluated using a series of permutation tests.

Results

A total of 717 questionnaires was received from 29 of the 33 anesthesia resident teaching programs solicited. The participating institutions are listed in the Appendix. The questionnaires returned were analyzed according to category of the evaluating personnel. Because of the relatively few PGY-1 respondents ($n = 25$) and because 7 of the 12 books evaluated by this group received less than 16% of the total scores, data from this group were omitted from further calculations. About half (16 of 29) of the programs provided data in the nurse category. Respondents in this category included both student nurse anesthetists and CRNAs. Subjective ratings based on questionnaire scores for each category of personnel are shown in Table 2.

The total number of respondents in each personnel category is shown with the corresponding rank coefficient in Table 3. A statistically significant positive correlation ($P < 0.01$) was found between the subjective and objective evaluations for the total group, as well as for each subgroup. No statistically significant difference was found between subgroups of respondents.

Discussion

The criteria used to rank anesthesia textbooks according to currency scores follow the method described by Pittinger (1). This technique analyzes the currentness of bibliographic references relative to the copyright dates of the texts in which references were cited. Briefly, for each text, the mean, the median, and the mode were calculated for the dates of all references tabulated at yearly intervals. To characterize a composite central tendency for each text, these values were combined into a single statistic, the geometric mean (vintage index), which is the cube root of the product of the mean, the median, and the mode. The currency score, a measure of up-to-dateness relative to copyright date of the source text, was calculated as 1000 times the reciprocal of the difference between copyright date and the vintage index.

The subjective evaluation of usefulness or value of 12 textbooks selected by anesthesia residents, nurses, and faculty as indicated in the questionnaire scores correlates well with the objective evaluation of up-to-dateness as judged by currency scores. Although the number of responses from PGY-1 residents was inadequate for statistical analysis, 60–96% (mean, 80%) of the respondents evaluated books 7 through 11, the same five texts that were ranked highest by all the other respondents. Whether or not the subjective rating of anesthesia personnel in private practice is sim-

Table 3. Number of Respondents and Rank Coefficients for the Correlation Between Questionnaire and Currency Scores According to Each Category of Anesthesia Personnel, Taken from Table 2

Category	Number	r Value[a]
PGY-2	110	0.631
PGY-3	121	0.698
PGY-4	40	0.706
Nurse anesthetists	82	0.504
Anesthesia faculty	339	0.580
All respondents	692	0.636

[a] $P < 0.01$ for all r values.

ilar to academic readers was not elucidated by this study.

The assessment of currentness is only one of many attributes that contributes to the value of a textbook. Other factors such as subject matter, clarity, and conciseness make textbooks useful to students of anesthesiology. This survey analysis showed a statistically significant correlation between the subjective assessment of usefulness or value and the objective method of evaluating the currency of references relative to copyright date. The study corroborates the predictive value of the objective scoring system.

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Appendix

List of Participants

Bowman Gray School of Medicine
Brigham and Women's Hospital
Case Western Reserve University
Duke University Medical Center
Emory University School of Medicine
Indiana University Medical Center
Massachusetts General Hospital
Mayo Clinic
Oregon Health Sciences University
Stanford University Medical Center
University of Alabama at Birmingham
University of Arizona College of Medicine
University of California, Davis
University of California, Los Angeles
University of California, San Francisco
University of Colorado School of Medicine
University of Connecticut Health Center
University of Florida
University of Iowa
University of Kentucky
University of Miami School of Medicine
University of Minnesota Hospital
University of North Carolina
University of Texas, Medical Branch
University of Virginia Medical School
VA Medical Center, Philadelphia, Pennsylvania
VA Medical Center, San Diego, California
Vanderbilt University Hospital
Wilford Hall USAF Medical Center

Clinical Reports

Transient Aphonia and Quadriplegia during Epidural Anesthesia

H. Drexler, MD, S. Zaroura, MD, Y. Shapira, MD

Most of the reported neurological complications of epidural or spinal anesthesia primarily affect the lower extremities (1). We report an unusual complication of aphonia and quadriplegia that occurred during epidural anesthesia.

Case Report

An 81-yr-old woman was admitted to the hospital with a fracture of the left femoral neck resulting from a fall 2 hr before admission. On admission the patient was well oriented and very talkative. Her height was 150 cm and weight 55 kg. Nutrition and hydration were good. Blood pressure was 160/90 mm Hg, and her pulse was 88 beats/min and regular. Physical examination revealed a 2/6 systolic murmur at the apex. The lungs were clear on auscultation. Neurological examination was normal. The ECG showed evidence of an old inferior myocardial infarction, left ventricular hypertrophy, and inverted T waves in the precordial leads. X-ray of the pelvis showed a pertrochanteric fracture of the left femur. Past history included insertion of a Moore's prosthesis in the right femur; ischemic heart disease for the past ten years, treated with digoxin (0.125 mg/day), furosemide (40 mg/day), and isosorbide dinitrate (10 mg/day); inferior wall myocardial infarct six years before; and a temporarily confused state after the death of a relative two years earlier.

Because of her relatively good general condition and her previously active state, it was decided to insert a Moore's prosthesis, which would allow subsequent rapid ambulation. As is common practice in our hospital, it was decided to use epidural anesthesia for the proposed procedure.

On arrival in the induction room, an ECG monitor was applied, oxygen (4 L/min) was administered by mask, and blood pressure (160/100 mm Hg) and pulse (90 beats/min) were measured. Hartmann's solution (1000 ml) was infused intravenously fairly rapidly before induction of anesthesia.

The patient was positioned laterally on the affected hip and the table was placed in slight head-up position. Blood pressure and pulse remained unchanged. The patient, despite being in pain, was most cooperative and remained extremely talkative. A Tuohy 16 gauge needle was inserted through the L1–L2 space, the epidural space being identified by loss of resistance. Then, 2 ml of 0.5% bupivacaine without epinephrine was injected. After 4 min, another 8 ml was injected with the patient still lying on the affected side. After 7–8 min she complained of nausea, systolic blood pressure decreased to 120 mm Hg, and the pulse decreased to 60 beats/min. The patient did not complain of breathlessness and there were no signs of respiratory distress. At the same time it was noticed that she was unable to speak. She was immediately returned to the supine position and ephedrine (10 mg) and atropine (0.25 mg) were injected intravenously. After this, she remained unable to speak. She tried but could not emit any sound. She moved her lips and tongue, mouthing the words she wanted to say and she understood fully all that was said to her.

She remained conscious all that time. No neurological deficit was apparent in the cranial nerves except for the aphonia. In addition, she was unable to move her upper extremities due to a flaccid paralysis. Her lower extremities were also paralyzed, but this we expected due to the regional anesthetic. The level of sensory anesthesia could not be determined with precision because of the difficulty of proper communication with the patient, but she appeared to respond to pinprick in the cranial nerves area. The decreases in blood pressure and pulse rate were not excessive and there was no respiratory distress to give

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Address correspondence to Dr. Drexler, Anesthesia Department, Bikur Holim Hospital, POB 492, Jerusalem, Israel.

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evidence of a high level of anesthesia due to phrenic nerve involvement. Blood pressure and pulse returned gradually within 3–5 min to preanesthetic levels. Twenty-five minutes after the injection of the bupivacaine, her voice started to return, as did the ability to move her arms.

Because blood pressure, heart rate, and ECG remained stable, the neurological deficits improved and anesthesia of the lower extremities was good, it was decided to proceed with the operation, which lasted 45 min and was uneventful. Full recovery took place and no neurological deficit was observed after regression of anesthesia.

Discussion

A patient is presented who developed unusual neurologic findings outside the area of epidural anesthesia. The deficit consisted of aphonia and flaccid paralysis of both upper extremities. Because the exact level of the epidural anesthesia could not be determined, the paralysis of the upper extremities could be attributed to the direct effect of the anesthetic reaching a spinal level of C5. It is unlikely that the anesthetic reached beyond this level, because phrenic nerve function—as evidenced by normal breathing—was not compromised. However, it is also possible that the anesthetic did not reach even the level of T1. This leaves the paralysis of the upper extremities to be explained by some other mechanism. The most likely explanation is a short transient ischemic episode involving the vertebrobasilar circulation. Ischemia in the area supplied by the vertebral arteries before they enter the basilar artery can explain the quadriplegia and the vocal cord paralysis with simultaneous sparing of the other cranial nerves (e.g., facial, hypoglossal). The ischemia can be explained as secondary to the transitory decrease in blood pressure. The patient remained awake and alert, able to ventilate adequately and to move her eyes, lips, and tongue in a purposeful manner, thus excluding alteration in consciousness, which would be associated with a higher level of brainstem ischemia.

The possibility of ischemia in the circulation of the anterior cerebral cortex is unlikely. In view of the bilaterality of the neurological findings, one would have to consider ischemia in the distribution of both internal carotid arteries. Although proximal diplegia can be seen in transient ischemia affecting the watershed areas of the cerebral cortex between the areas supplied by the anterior and middle cerebral arteries, the aphonia cannot be explained on this basis. Another explanation, which cannot be ruled out, is a psychophysical reaction (conversion reaction or hysteria). Aphonia and transient paralysis are not uncommon manifestations of hysteria.

The possibility of a convulsive disorder is unlikely in view of uneventful past history, absence of tonic–clonic movements, and no loss of consciousness. Transient quadriplegia with aphonia has not been reported as a complication of epidural anesthesia, to the best of our knowledge.

Prolonged neurological sequelae after epidural or spinal anesthesia are rare. An extensive review of the literature by Dawkins (1) indicates that long-lasting paralysis occurs infrequently after lumbar or thoracic epidural block. Transient paraplegia beyond the time allowed for by the anesthetic itself was reported in 0.1% of cases, whereas only 0.2% suffered permanent paraplegia. In his own series of 4000 epidural blocks, Dawkins had one case of permanent paraplegia and one patient who suffered paresis that improved over 2 months.

Four cases of prolonged neurological deficit after attempted epidural block with chloroprocaine were recently reported (2,3). Two patients had persistent motor paralysis of lower extremities; in the other two, total spinal anesthesia occurred, requiring artificial ventilation during the operation. In addition, motor paralysis of the lower extremities was noted after regression of anesthesia in both patients, accompanied by urinary and fecal incontinence and partial sensory loss in one patient. Kane, in a review of the literature on neurological deficits after epidural or spinal anesthesia (4), found only one case with quadriparesis (5). This patient died seven days after the procedure and autopsy revealed necrosis of central grey matter of cord, attributed to shock during operation. In our case, the quadriparesis was of a very short duration, suggesting a transient ischemic attack in the vertebrobasilar vascular system, most likely secondary to the hypotension that occurred during the procedure.

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Seizure Activity during Isoflurane Anesthesia

Jayson A. Hymes, MD, MPH

Seizure activity under general anesthesia is an uncommon phenomenon. EEG abnormalities as well as tremors, clonus, and frank seizure-like motor activity have been reported with the use of enflurane, especially in higher doses and with concomitant hypocarbia (1). Recently several anecdotal reports have indicated fentanyl as a possible etiologic factor in the occurrence of intraoperative seizure activity. One of the purported benefits of the use of isoflurane as a general anesthetic is its rendering of an isoelectric EEG at concentrations greater than 1.8% in expired air and the resultant cerebral protection that this implies (2). We have observed intraoperative myoclonus and seizure-like activity in a patient during general anesthesia produced by isoflurane.

Case Report

A 27-yr-old, ASA class II, 205-cm tall, 91-kg male was scheduled for anterior synovectomy of the left hip for painful osteocondromatosis. Past medical history included poliomyelitis at 3 years old with residual atrophy of his left shoulder muscles and some thoracic scoliosis. The latter was not severe enough to impair ventilation. Past surgical history was notable for a previous orthopedic procedure on his left hand approximately 10 yr prior to this admission. General anesthesia of an unknown type was administered and no complications were reported. Physical examination was within normal limits, except for some wasting of his left shoulder musculature and mild thoracic scoliosis. Preoperative neurological examination was within normal limits.

The patient was taken to the operating room after a premedication with oral diazepam (10 mg), intramuscular morphine (10 mg), and glycopyrrolate (0.2 mg). The patient was adequately sedated. An intravenous infusion was begun and ECG electrodes and a blood pressure cuff were applied. The patient was given 100 μg of fentanyl and 3 mg of *d*-tubocurarine and breathed 100% oxygen for 3 min before thiopental (400 mg) and succinylcholine (120 mg) were injected. The trachea was intubated without difficulty. The patient then received nitrous oxide 70% in oxygen and isoflurane. Isoflurane concentrations in the inspired gas initially ranged from 3 to 5%, but then were maintained at 0.75% with a fresh gas flow of 2.5:1 ($N_2:O_2$). Ventilation was controlled (1000 ml × 8 breaths/min) and the inspired concentration of oxygen (30%) as well as end-tidal P_{CO_2} (38 mm Hg) were continuously monitored. The surgeons commented that the patient was becoming "tight" and they felt that the patient's muscle tone increased as the operation progressed. There were no sympathetic signs of light anesthesia; the patient's blood pressure and pulse rate remained unchanged, and sympathetic responses to noxious stimulation were suppressed. Approximately 1.5 hr after induction, the patient was given another 100-μg dose of fentanyl because of an increase in systolic blood pressure from approximately 95 to 115 torr. Approximately 30 min later, the surgeons noted that the increased muscle tone of the left lower extremity had progressed to sustained monoclonus of the left foot upon movement of the left leg. Examination of the patient at that time revealed sustained myoclonus in all four extremities and mild muscle spasticity in the trunk and limbs. The pulse rate, blood pressure, and normal peak inspiratory pressures remained unchanged. End-tidal P_{CO_2} at the time was approximately 34 mm Hg and the oropharyngeal temperature was 35°C. Within 5 min the myoclonus that had been observed only with surgical stimulation suddenly progressed to a generalized seizure involving the musculature of the extremities, abdomen, trunk, and face. No evidence of a Jacksonian focus was seen as the movement appeared to develop over the entire body simultaneously. Thiopental (150 mg) was administered intravenously, and the muscular activity stopped within 1 min. Arterial blood-gas tensions at this time were P_{O_2} 167 mm Hg and P_{CO_2} 52 mm Hg; pH was 7.33 with a base excess +1, and serum electrolytes were within normal limits, including ionized calcium (2.2 mEq/L). The end-tidal P_{CO_2} was slightly

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Received from the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia. Accepted for publication November 5, 1984.

Address correspondence to Dr. Hymes, Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA 30322.

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increased from the previous value, to approximately 58 mm Hg.

After this episode, the patient continued to have sustained myoclonus in all extremities. Babinski reflexes were absent bilaterally. The myoclonus continued until the end of the operation, approximately 35 min later. The patient was observed closely during emergence from anesthesia and, as the isoflurane concentration in expired gas decreased, the myoclonus was confined to the lower extremities and its duration decreased to approximately 6–10 beats. The patient was awake and alert before leaving the operating room. He was extubated and transferred to the recovery room. He continued to respond appropriately and remained normal in every aspect except for persistent myoclonus. There was no evidence of inadequate sphincter function or slowness in awakening. He was discharged from the recovery room after 1 hr with 2–3 myoclonic contractions per minute involving both lower extremities. By that evening the patient's neurological examination had returned to normal. At this time an EEG was also normal. The patient was discharged home in stable condition after 5 days. Further discussions with the patient and his family members failed to elicit personal or familial histories of neurological problems.

Discussion

Electroencephalographic recordings were not obtained during the maximum seizure-like activity exhibited by this patient. Observations by the surgical and anesthetic personnel were consistently described as generalized seizure-like activity in an otherwise well-anesthetized patient. Monitoring of inspired oxygen concentration, end-tidal P_{CO_2}, and hemodynamic variability revealed no problems and provided no clue as to etiologic factors. Blood-gas tensions immediately after the most intense activity were essentially normal except for a mild increase in arterial P_{CO_2} that was matched by a mild increase in end-tidal P_{CO_2}, possibly suggesting increased CO_2 production.

One possible confusing factor is that the patient had received fentanyl in two 100-μg intravenous boluses, the first having been administered approximately 12.75 hr prior to the apparent seizure, and the second approximately 1.5 hr prior to the event. Even though seizures have been implicated as a consequence of high doses of fentanyl, only anecdotal reports and no EEG evidence of seizures have been published (3). The very small doses of fentanyl used in this case, coupled with the long time between the administration of fentanyl and the onset of myoclonus serve to discount the possibility of fentanyl as a causative factor.

Other possible seizure-precipitating factors to be considered are abnormalities of serum electrolyte levels and P_{CO_2}. These were within normal limits at the time of the seizure-like activity. Another conceivable cause of the increased muscle tone early in the case might have been the skeletal muscle effects of malignant hyperpyrexia. However, the lack of change in hemodynamic and metabolic variables (pulse rate, blood pressure, and temperature) and respiratory values (respiratory rate, end-tidal P_{CO_2}) are against this possibility. The patient's history of poliomyelitis might contribute to the perception of abnormal muscular activity under general anesthesia. Two separate neurological consultations after the operation expressed that this was a very remote possibility.

In summary, the otherwise healthy young man had an apparent grand mal seizure under O_2–N_2O and isoflurane anesthesia with preceding and subsequent myoclonus that resolved after the discontinuation of the anesthetics. Even though isoflurane has been thought to be superior to its isomer enflurane, in this regard (1,2,4,5) it may not be devoid of CNS-stimulating actions, at least in some types of patients.

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Atracurium in a Child with Myotonic Dystrophy

Joseph A. Stirt, MD, David J. Stone, MD, Guy Weinberg, MD, Douglas F. Willson, MD, Cary S. Sternick, MD, and Michael D. Sussman, MD

"The production of muscle relaxation in a myotonic is one of the most difficult problems facing the anesthesiologist" (1). Succinylcholine has been shown to cause prolonged contracture of skeletal muscle in patients with myotonic dystrophy (2). Intubating doses of pancuronium, *d*-tubocurarine, or metocurine, the most commonly used nondepolarizing relaxants, may produce a duration of neuromuscular block requiring antagonism after a relatively brief surgical procedure. Little information exists about the effects of neostigmine in patients with myotonic dystrophy (2,3). We describe here the use of atracurium for intubation and muscle relaxation in a 3-yr-old child with myotonic dystrophy.

Case Report

A 3-yr-old 15-kg girl was admitted to the hospital for bilateral Achilles tendon lengthening. A diagnosis of myotonic dystrophy had been made previously by a pediatric neurologist and a medical geneticist on the basis of history, physical examination, and electromyography. The patient's mother and maternal grandfather also had myotonic dystrophy.

Physical examination revealed a child with generalized hypotonia, moderate scoliosis of the thoracic spine, and severe plantar flexion of the feet. Other than esotropia and decreased visual acuity in the left eye, no abnormalities of the head and neck were noted. Laboratory values included a hematocrit of 42 and a normal urinalysis.

The patient was brought to the operating room without premedication. Use of the prone position for surgery was planned. Mask induction with halothane in O_2 was without incident. An intravenous infusion of 5% dextrose in lactated Ringer's solution was begun and 0.1 mg of atropine administered intravenously. A Grass FT-10 force transducer was attached to the hand to monitor twitch tension of the thumb in response to supramaximal ulnar nerve stimulation of 0.15-msec duration at 0.15 Hz. A Gould strip chart recorder run at 5 mm/min was used to record the force transducer measurements.

Atracurium 1.5 mg (0.1 mg/kg) was given intravenously, and the onset of neuromuscular block began within 1 min. A 92% reduction in twitch height occurred within 4 min (Fig. 1). Laryngoscopy and intubation were performed without difficulty 6 min after atracurium administration. No myotonia or patient movement occurred during laryngoscopy or intubation. At this time the surgeon decided to leave the patient supine for better surgical access.

Anesthesia was maintained with halothane and 60% N_2O in O_2 using a humidified, warmed circle system for the duration of the operation; recovery from neuromuscular block was allowed to occur spontaneously. Recovery to 95% of control twitch height occurred 54 min after atracurium administration (Fig. 1). After the patient emerged from anesthesia, the trachea was extubated once airway reflexes had returned. The child subsequently made an uneventful recovery.

Discussion

Myotonic dystrophy, also known as dystrophia myotonia, dystrophia myotonica, myotonia atrophica, Batten–Curschmann disease, Steinert's disease, and Hoffman's disease, is a rare autosomal dominantly inherited congenital disorder. It is a steadily progressive muscular disorder characterized by myotonia, a delay in the relaxation of contracted muscle, and progressive muscular atrophy and wasting (4). Multisystem organ involvement, especially of the airway and swallowing mechanism (5,6), heart (4,7), and lungs (4,8), is commonly present, rendering anesthesia for such patients difficult. Onset of the disease is usually

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Received from the Departments of Anesthesiology, Pediatrics, and Orthopedics, University of Virginia Medical Center, Charlottesville, Virginia and the Department of Neurology, Tomball Community Hospital, Tomball, Texas. Accepted for publication October 19, 1984.

Address correspondence to Dr. Stirt, Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, VA 22908.

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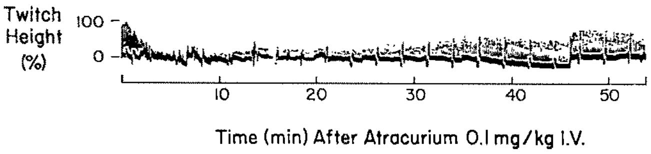

Figure 1. Neuromuscular block after atracurium (0.1 mg/kg intravenously). Onset of block began within 1 min, and 92% reduction in twitch height occurred in 4 min. Recovery to 95% of control twitch height occurred 54 min after administration of atracurium.

in late childhood or adult life, but in recent years the syndrome has been described in newborns and infants (9). "Little is known of the way pediatric patients with early onset myotonic dystrophy respond to anesthesia" (10).

Several factors influenced our approach to the patient we describe above. First, because the prone position was to be employed, we considered tracheal intubation to be mandatory to assure an airway. Intubation probably could have been performed after inhalation anesthesia induction without the aid of muscle relaxants. However, triggering of a myotonic response after attempts at airway instrumentation without muscle relaxation, preventing successful establishment of an airway, ventilation, or both, has been reported (2). Thus we thought that intubation with the help of a muscle relaxant was optimal for our patient.

A rapid sequence induction and intubation did not seem appropriate because structural airway abnormalities may be present in patients with myotonic dystrophy (6) and because succinylcholine produces a generalized contracture of skeletal muscle in these patients, resulting in inability to maintain an airway and to ventilate the lungs (2). In addition, establishment of an intravenous infusion in our awake patient would have been difficult. The response of myotonic patients to nondepolarizing relaxants, however, appears to be normal (2), although mechanical stimulation may produce contracture (11). Because the length of the planned procedure was estimated to be approximately one hour, intubating doses of the longer acting nondepolarizing relaxants most likely would have required antagonism with an anticholinesterase drug at the conclusion of surgery, unless the patient had been left intubated until spontaneous recovery had occurred.

Use of neostigmine in myotonic dystrophy has been reported safe in two cases (2), although an earlier report mentions the possibility of increased myotonia after neostigmine (3). We chose to try to avoid neostigmine because of the limited information on its effects in these patients.

In summary, we used atracurium to provide neuromuscular block for intubation and surgery in a 3-yr-old child with myotonic dystrophy. Muscle relaxation and spontaneous recovery in less than one hour were without incident. Atracurium, because of its shorter duration of action and, therefore, less likely need for antagonism, appears to offer an alternative to other muscle relaxants in those patients with myotonic dystrophy who require neuromuscular blockade during anesthesia.

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Anesthetic Management of a Patient with Moebius Syndrome

William J. Krajcirik, DO, Isaac Azar, MD, Sheldon Opperman, MD, and Erwin Lear, MD

Moebius syndrome is a rare congenital dysplasia of cranial nerves (1,2). The VI and VII cranial nerves are commonly affected, resulting in esotropia and complete or partial facial paralysis. Occasionally the V, X, XI, and XII cranial nerves are also involved, resulting in difficulties in chewing, swallowing, and coughing, and often leading to aspiration with respiratory complications. The following is a report of the anesthetic management and postoperative complications in a patient with Moebius syndrome.

Case Report

A 13-yr-old girl with Moebius syndrome and recurrent pulmonary aspiration was scheduled for diagnostic fiberoptic bronchoscopy because of persistent left lower lobe pneumonia. Previous examination by a neurologist revealed expressionless facies, marked bilateral facial paralysis, and dysarthria. She could not gaze fully to right or left. The gag reflex was present, but elevation of the uvula was very poor. The corneal reflex was impaired bilaterally.

Two years prior to the present admission, the patient had an episode of chest pain, tachycardia, and pleuritic and pericardial friction rubs. The ECG revealed left axis deviation with low voltage, and echocardiography suggested an increase in the left ventricular size. The possibility of cardiomyopathy was entertained. Shortly after these events the patient underwent uneventful arthroscopy under anesthesia with nitrous oxide, fentanyl, and pancuronium.

At the present admission physical examination revealed a slender girl weighing 26 kg. The heart rate was 88 beats/min, blood pressure 100/70 mm Hg, respiratory rate 18 breaths/min, and body temperature 37°C. Examination of the chest revealed diminished breath sounds at the left lower base. A II/VI systolic murmur was heard at the apex, occasionally associated with a heave. Echocardiographic studies suggested decreased left ventricular contractility and were compatible with cardiomyopathy. Chest x-rays revealed left lower lobe atelectasis and pneumonia. The arterial blood-gas tensions while the patient was breathing room air were P_{O_2}, 71 mm Hg; P_{CO_2}, 40 mm Hg; and pH, 7.39. Other routine studies were within normal limits.

No preanesthesia sedation was given. In the operating room an intravenous catheter was inserted and a precordial stethoscope, blood pressure cuff, ECG electrodes, and a peripheral nerve stimulator were applied. After oxygenation by mask, anesthesia was induced with fentanyl (0.1 mg) and diazepam (10 mg intravenously). Pancuronium (0.75 mg) and *d*-tubocurarine (4.5 mg) were given to facilitate tracheal intubation. An 8.0-mm tracheal tube was placed easily. Anesthesia was maintained with 50% nitrous oxide in oxygen and intermittent doses of fentanyl. Ventilation was maintained manually with tidal volume of 250 ml at the rate of 12 breaths/min.

Copious secretions were aspirated via the bronchoscope, but no specific cause for the atelectasis was found. The bronchial tree was irrigated with saline and the bronchoscope was withdrawn. The patient's vital signs remained stable. At the conclusion of the procedure, edrophonium (15 mg) and atropine (0.4 mg) were administered to reverse the neuromuscular blockade. The train-of-four response indicated complete reversal of the neuromuscular blockade and the patient's spontaneous breathing was deemed adequate clinically. After vigorous aspiration of secretions through the tracheal tube, the patient was extubated and transferred awake to the recovery room.

Shortly after arrival in the recovery room, the patient developed acute respiratory distress. Examination of the chest revealed bilateral diffuse coarse bronchi. Arterial blood gases, determined with the patient breathing oxygen by mask, were P_{O_2}, 64 mm Hg; P_{CO_2}, 70 mm Hg; and pH, 7.27. The trachea was intubated again and, after aspirating large amounts of secretions through the tube, ventilation was mechanically controlled. Excessive production of secretions continued to occur and the patient required tracheal

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Adddress correspondence to Dr. Krajcirik, Department of Anesthesiology, Beth Israel Medical Center, Mount Sinai School of Medicine, New York, NY 10003.

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toilet and respiratory support for 48 hr. The patient was then weaned from the ventilator and the trachea was extubated without further complications.

Discussion

Our patient had several anesthetic problems. First, she had a weak swallowing reflex and recurrent pulmonary infections, probably from repeated episodes of aspiration. This resulted in acute and chronic pulmonary changes and a reduction in pulmonary function, as evident from her preanesthetic chest x-ray and by arterial blood-gas values. Also, though Moebius syndrome has not been associated with cardiomyopathy, our patient had a medical history suggestive of cardiomyopathy. However, because myopathies are often associated with a cardiomyopathy (3), it is possible that this patient's cardiac symptoms were part of the syndrome. We avoided volatile anesthetic agents to reduce the risk of myocardial depression. The patient tolerated diazepam and fentanyl well and no major changes in the blood pressure occurred during the procedure.

Tracheal intubation was facilitated by a mixture of pancuronium and *d*-tubocurarine in order to reduce the cardiovascular effects of a fully paralyzing dose of either drug (4). In addition, the mutual potentiation of pancuronium and *d*-tubocurarine (5) reduced the total intubating dose of the mixture and allowed rapid recovery of the neuromuscular junction. At the conclusion of the bronchoscopy, the neuromuscular blockade was rapidly reversed after edrophonium administration.

The only complication in this patient was the accumulation of copious secretions in the airway after extubation. This was probably caused by the lack of adequate swallowing and coughing reflexes, and was probably further aggravated by instrumentation of the airway and administration of edrophonium. The preoperative use of antisialagogues such as atropine, scopolamine, and glycopyrrolate may have minimized the secretions. The patient should have been left intubated after anesthesia until the bronchial secretions diminished to the point that the patient could manage them herself.

In summary, a patient with Moebius syndrome and repeated episodes of aspiration and pulmonary complications tolerated well nitrous oxide–fentanyl anesthesia with a *d*-tubocurarine–pancuronium mixture, during fiberoptic bronchoscopy. However, after the bronchoscopy the patient developed acute respiratory failure due to excessive secretions in the airway and required tracheal intubation and respiratory support for 48 hr. We recommend that these patients be medicated preoperatively with an antisialagogue and receive intensive respiratory support postoperatively, preferably with the tracheal tube in place, to facilitate bronchial toilet.

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Shoulder Block Anesthesia for Shoulder Reconstruction Surgery

David O. Peterson, MD

Effective regional anesthesia for glenohumeral arthroplasty must include blockade of the brachial plexus, the superficial cervical plexus, and the first through third thoracic somatic nerves. A shoulder block technique including interscalene and upper thoracic paravertebral blocks was developed for shoulder reconstruction procedures at the author's institution. Because the success rate and morbidity associated with this combination anesthetic are unreported, a retrospective analysis of one year's experience was undertaken.

Methods

Shoulder block was selected as the anesthetic technique including interscalene and upper thoracic paravertebral blocks was developed for shoulder reconphysical status I or II and ranged in age from 18 to 74 yr, with a mean age (± SD) of 24 ± 10 yr. Premedication was with a sedative or narcotic, or both. Blocks were performed in an induction room by a resident or other anesthesia trainee, with a staff anesthesiologist in attendance. Interscalene blocks were performed as described by Winnie (1), using a solution of 0.2–0.25% tetracaine and 0.375–0.4% lidocaine with 1:250–266,000 epinephrine.* Initial interscalene anesthetic doses were 41 ± 6 ml. Seventeen of 58 patients (29%) received a second injection of 29 ± 8 ml prior to the operation. There was no relationship between the volume or concentration of the initial injection and requirement of a second dose.

Paravertebral blocks as described by Moore (2) and Adriani (3) were performed at some or all of the C8–T4 levels using 3–15 ml (usually 5 ml) of the above solution per level. In 80% of cases T1–3 was blocked. T2 was included in all instances. Total doses were 21 ± 10 ml.

The total amount of anesthetic solution required for complete shoulder block averaged 71 ± 18 ml, corresponding to 271 ± 69 mg of lidocaine and 168 ± 43 mg tetracaine. Surgical techniques for glenohumeral joint arthroplasty in the semisitting position were as follows: Bristow (4)—38%, Bankart (5)—28%, Putti–Platt (6)—5%, unspecified—29%. Duration of surgery averaged 110 ± 38 min (range 35–225 min).

Results

There were two failed blocks (3.4%); both patients complaining of pain on initial skin incision. These patients then received general anesthesia. In none of the remainder did a block wear off or require intraoperative reinjection. There were no anesthetic complications. Patients were discharged directly from the operating suite to their wards.

One patient had postoperative biceps weakness and was found to have a transient isolated musculocutaneous nerve palsy, documented on electromyography. The attending surgeon attributed this to surgical traction on the nerve. Otherwise, no complications were reported in the postoperative notes.

Discussion

Shoulder surgery requires anesthesia of the nerves supplying the glenohumeral joint and the overlying skin in a wide area (Table 1). Branches from the brachial plexus, including the axillary, suprascapular, and lateral pectoral nerves innervate the joint capsule itself. Cutaneous sensation is supplied largely by supraclavicular (C3–4) branches of the cervical plexus, which cover a cape-like area over the shoulder (Fig. 1). Hence, the interscalene cervical–brachial plexus block would seem ideally suited for complete shoulder anesthesia. Yet in the only published study of

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The opinions or assertions expressed in this paper are those of the author and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or the naval service at large.

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Address correspondence to Lt. D. O. Peterson, MC, USNR, c/o Clinical Investigation Department, Naval Hospital, San Diego, CA 92134.

*Two solutions were used: compunding 1% tetracaine with 0.5% lidocaine (1:200,000 epinephrine) in a 1:3 or 1:4 ratio, resulting in either 0.25% tetracaine:0.375% lidocaine (1:266,000 epinephrine) or 0.2% tetracaine:0.4% lidocaine (1:250,000 epinephrine).

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Table 1. Components of the Shoulder Block

Area anesthetized	Nerve	Root	Block technique
Joint capsule	Axillary (BP)	C5–6	Interscalene
	Suprascapular (BP)	C5–6	Interscalene
	Lateral pectoral (BP)	C5–7	Interscalene
Shoulder "cape"	Supraclavicular (CP)	C3–4	Interscalene
Lower deltoid	Axillary (upper lateral brachial cutaneous) (BP)	C5–6	Interscalene
Chest wall	Intercostal	T1–3	Paravertebral
Axilla	Intercostobrachial	T2–3	Paravertebral
	Intercostal	T1–2	Paravertebral
	Medial brachial cutaneous (BP)	C8–T1	Interscalene

Abbreviations: BP, brachial plexus; CP, cervical plexus.

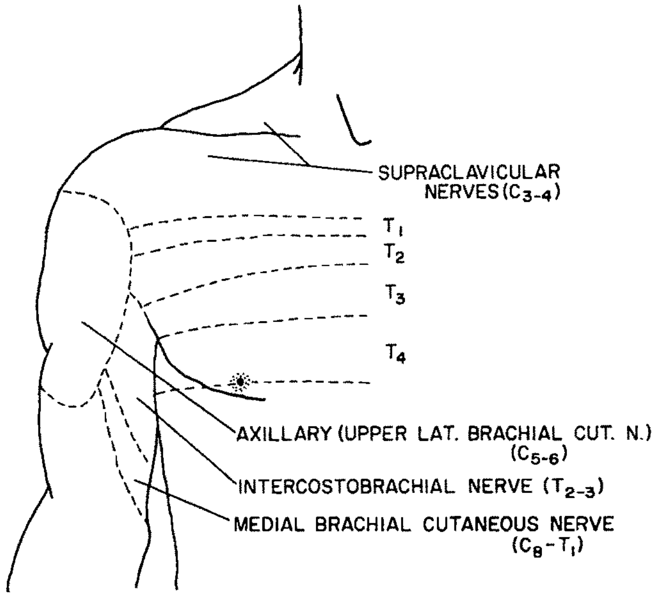
SUPRACLAVICULAR NERVES (C_{3-4})
T_1
T_2
T_3
T_4
AXILLARY (UPPER LAT. BRACHIAL CUT. N.) (C_{5-6})
INTERCOSTOBRACHIAL NERVE (T_{2-3})
MEDIAL BRACHIAL CUTANEOUS NERVE (C_8-T_1)

Figure 1. Cutaneous sensory innervation of the shoulder relevant to the performance of shoulder block anesthesia.

regional anesthesia for shoulder reconstruction surgery, Mitchell et al. (7) reported a failure rate of 15% in 46 patients who had only interscalene blocks.

In shoulder reconstruction, the surgical incision frequently extends beyond the cervical plexus "cape," and may reach almost to the axilla for a Bankart procedure. Also, retractors are placed deeply in the wound. Areas supplied by either the upper thoracic somatic nerves on the upper chest wall or the intercostobrachial nerve (T2–3) in the axilla will be affected. Both Adriani (3, pp 428–9) and Moore (2, p 236) recognized the significance of T2–3 for shoulder surgery and advocated axillary subcutaneous infiltration to peripherally block the intercostobrachial nerve. Raj (8) suggested intercostal blockade of T2 at the posterior axillary line. At this location, the T3 contribution of the intercostobrachial nerve might already have joined T2, but cutaneous branches from T3 may not all be adequately blocked, and the small T1 intercostal is altogether ignored.

A combination of T1–3 paravertebral blocks and interscalene block provide generous chest wall anesthesia and block with certainty both the T2 and T3 components of the intercostobrachial nerve. In this series, some patients also had C8 or T4 blocks, or both. The additional blocks were done to assure anesthesia of T1–3 roots in cases where the landmark spinous process of the "vertebra prominens" (C7) could not be differentiated from T1 with certainty.

In 1971 Balas (9) reported 300 cases using the subclavian perivascular block for a variety of operative procedures on the shoulder or upper arm. In those involving the shoulder capsule or axilla, T2 was blocked separately via the paravertebral approach. He reported an overall 4.67% incidence of failed block. In 1981 Dekrey and Balas (10) expanded Balas's series to more than 1500 upper arm and shoulder operations in which subclavian perivascular or interscalene blocks were used combined with paravertebrals when needed. However, in their report, specifics regarding techniques, operative procedures, and complications are lacking.

A failure rate of 3.4% for shoulder block compares favorably with the 4.6% rate seen by Balas (9) and the 15% failure rate of Mitchell (7). In the two failed blocks the patients complained of pain on initial incision, which indicates that the interscalene components were probably not adequately performed and tested. In a series of 34 interscalene blocks alone for various procedures, Ward (11) reported a 9% failure rate. In Winnie's (1) original study, he failed in 6%.

Although none was seen in this series, there are some potentially serious complications of shoulder block including pneumothorax (2,3,9,11,12), total subarachnoid block (13,14), high epidural block (15,16), and intravascular injection (2,3,7).

Systemic toxicity resulting from the use of excessively high concentrations and large volumes of anesthetic solution must be scrupously avoided. In this series, total tetracaine doses in excess of the commonly accepted limits for a single dose were sometimes used. The higher total doses were given in patients who required reinjection of one or more components of the shoulder block. Repeat injections should be performed only after an adequate period of time has elapsed since the initial dose, in order to allow the drug to have its effect and be partially metabolized, thus avoiding the high plasma anesthetic levels that would be seen after a single bolus injection of the same amount. Nevertheless, the means for treating a systemic toxic reaction should always be at hand when using the doses of local anesthetic agent necessary for shoulder block.

Most patients who have an effective interscalene block will develop a transient Horner's syndrome (2,10–12,17). Many will also be hoarse due to unilateral recurrent laryngeal nerve block (10–12,17), and 5–6% will develop a unilateral phrenic nerve block (11,12,18). These latter nerve blocks are usually of little concern, and none were mentioned on the anesthetic records in this patient group, although some may have occurred.

Benefits associated with regional anesthesia cited by Mitchell (7) include significantly lower blood loss (presumably due to epinephrine-induced vasoconstriction) and shorter hospital stay. Regional anesthesia also provides analgesia in the postoperative period. Although we did not do so, a catheter can also be placed in the interscalene space (1), to provide for longer duration of operative anesthesia and postoperative analgesia, the latter for as long as several days, as reported in 25 patients by Dekrey (19). Use of the shoulder block technique avoids potential risks associated with general endotracheal anesthesia in a semisitting patient where the anesthetist has poor access to the airway.

In this study population comprised predominantly of young healthy patients, the shoulder block technique was safe and effective. Because relatively large doses of local anesthetic are routinely employed, caution should be used in patient selection and amount of anesthetic administered. It should also be established that the operative procedure is not expected to be unusually long, as anesthetic duration may not suffice and the patient may not be able to tolerate an immobile position for a long period. With these considerations taken into account, the shoulder block can be a valuable addition to the anesthesiologist's armamentarium.

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1985;64:376

Pulse Oximetry during Pulmonary Artery Surgery

Robert H. Friesen, MD

The pulse oximeter (Nellcor, Hayward, CA) is a noninvasive monitor that utilizes spectrophotoelectric techniques to measure arterial oxygen saturation (Sa_{O_2}) in a pulsating vascular bed such as that of a finger. The technique has been described and its accuracy in adults has been documented (1). Abstracts of current research indicate that the monitor is accurate in pediatric patients as well (2,3).

Surgical manipulations of the pulmonary artery (PA), such as application of a band or a clamp, can reduce PA blood flow enough that hypoxemia results. We are using the pulse oximeter for early detection of this complication. Two recent cases illustrate its use.

A 3-week-old term neonate had coarctation of the aorta and a single ventricular septal defect (VSD) associated with large left-to-right shunt, pulmonary hypertension, and congestive heart failure. The operation was repair of the coarctation followed by PA banding. Proper placement of a PA band usually results in a small decrease in arterial oxygen saturation due to variable shunting across the VSD. The optimal saturation range immediately following banding is 87–92% during ventilation with 100% oxygen (4). If the band is too tight, the reduction in pulmonary blood flow may be so great as to cause hypoxemia. When the PA band was initially placed in our patient, Sa_{O_2} decreased from 95 to 82%, indicating that the band was too tight. The band was adjusted until Sa_{O_2} was 90%. When banding was complete, systolic pressure in the main PA distal to the band was 56 mm Hg and in the right ventricle 98 mm Hg. Arterial blood-gases were satisfactory.

The second patient was a term neonate with pulmonary atresia. Prostaglandin E was infused to maintain patency of the ductus arteriosus and thus provide some PA blood flow. Sa_{O_2} was 75%. A Blalock–Taussig shunt was indicated to increase PA blood flow. During this operation, the right PA (RPA) is normally clamped to allow anastomosis of the distal end of the shunt to the side of the RPA. Most patients tolerate this temporary occlusion of RPA blood flow, but a few who do not become hypoxemic enough to experience cardiovascular deterioration. When the RPA was clamped in our patient, Sa_{O_2} fell to below 20% in 60–90 sec. The clamp was removed before deterioration of vital signs occurred, and Sa_{O_2} returned to 75%. The RPA was too small to be partially clamped, so the operation was completed by anastomosing the distal end of the shunt to the main PA using a partial main PA clamp, which did not reduce PA blood flow significantly. When the shunt was completed, Sa_{O_2} increased to 90%.

These cases illustrate the use of the pulse oximeter to rapidly detect and quantify oxygen desaturation during surgical manipulations that reduce PA blood flow. Traditionally, detection of this complication has depended on intraoperative recognition of the clinical signs of hypoxemia, such as bradycardia or cyanosis, or on arterial blood-gas analysis. The advantage of the pulse oximeter is that desaturation can be detected immediately, more quickly than laboratory methods and before clinical deterioration of the patient.

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Address correspondence to Dr. Friesen, Department of Anesthesiology, The Children's Hospital, Denver, CO 80218.

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Letters to the Editor

Disulfiram-like Reaction to Moxalactam after Celiac Plexus Alcohol Block

To the Editor:

We have recently observed a disulfiram-like reaction in a patient who had taken a β-lactam antibiotic and underwent celiac plexus block with alcohol.

A 68-yr-old woman suffering from abdominal and back pain of intractable nature secondary to uterine carcinoma underwent celiac plexus alcohol block. She had been given 2 g moxalactam intravenously daily for 14 days for pneumonia, the last dose being 3 days prior to the present procedure. Satisfactory pain relief was obtained immediately after injection of 15 ml of 67% alcohol into the paraaortic space. Approximately 10 min later, flushing and sweating appeared over the neck and chest, followed by dizziness, nausea, and vomiting. The arterial blood pressure decreased from 130/75 to 80/40 torr and the heart rate increased from 80 to 130 beats/min. The hypotension lasted for 4 hr despite fluid and vasopressor treatment. The other symptoms disappeared 8 hr later without sequelae.

The disulfiram-like action of β-lactam antibiotics, i.e., an inhibition of acetaldehyde dehydrogenase, was first speculated in human volunteers who took cefoperazone and alcohol; they developed abnormal reactions to alcohol intake, including peculiar facial flushing and tachycardia (1). The elevation of blood acetaldehyde level after combined administration of alcohol and β-lactams was confirmed in rats (2). The present case indicates that the disulfiram-like action of several antibiotics should be taken into consideration when alcohol block is attempted.

Shinichiro Umeda, MD
Toshiyuki Arai, MD
Department of Anesthesiology
Kyoto University Hospital
Sakyo-ku, Kyoto, Japan

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Esophageal Stethoscope Amplifier

To the Editor:

A device has been in use at University Hospital in Boston that amplifies the heart and breath sounds derived from an esophageal stethoscope (Fig. 1). The device frees the anesthesiologist from the earpiece that so frequently limits movement about the patient. The device also allows all anesthesia personnel in the room to monitor the patient's breath sounds simultaneously.

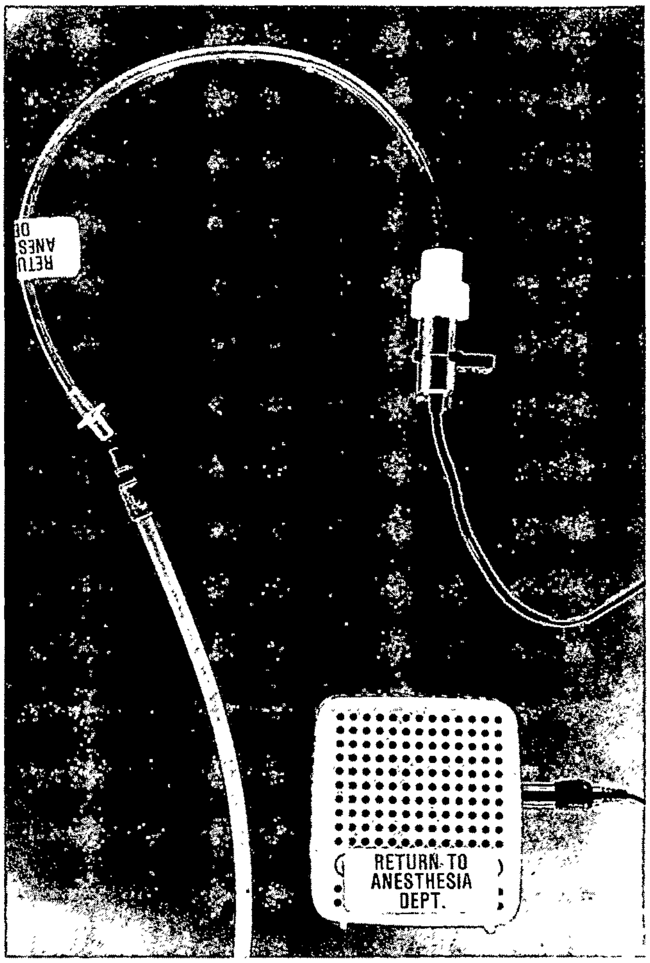

Figure 1. Esophageal stethoscope amplifier.

The device is simple to assemble, costs under $25, and the parts can be obtained easily. The device consists of a microphone (Radio Shack #33-1058), amplifier (Radio Shack #277-1008), an MA-1 thermometer adapter (Bennett #000422) that fits over the microphone, and a female Luer connector (Dupaco Hemocoil) that connects to the esophageal stethoscope.

Robert Douglass
Baburao Doddapaneni, MD
University Hospital
Boston University Medical Center
Department of Anesthesia
75 East Newton Street
Boston, MA 02118

Capnographs: A New Operating Room Pollution Hazard?

To the Editor:

Although the significance of exposure to anesthetic gases as an occupational health hazard remains controversial (1), the evidence for toxicity was sufficient to provoke recommendations from the National Institute of Occupational Safety and Health (NIOSH) (2). Current NIOSH standards for operating rooms suggest a maximum time-weighted average concentration of 25 ppm nitrous oxide and 1 ppm for the potent inhalational agents. Anesthesia departments, including our own, are currently employing control measures that include low-leakage equipment and efficient scavenging systems. We recently assessed a newly introduced device, the continuous CO_2 analyzer, for its environmental pollution potential.

Indirect monitoring of Pa_{CO_2} during anesthesia is easily and inexpensively accomplished with current infrared technology; the Puritan–Bennett CO_2 analyzer is a typical one. In practice, a sample port is inserted into the breathing circuit next to the endotracheal tube. Gas is sampled continuously; Puritan–Bennett suggests a flow rate of 150 ml/min (+25, −5) for optimal response time (3). The sample is exhausted through the rear panel of the monitor (Fig. 1). The position of the monitor itself, relative to the patient, is limited by the length of the sample tubing with a suggested maximum of 150 cm.

If the monitor samples a mixture of 1% halothane in 70% N_2O at a rate of 150 ml/min, the exposure concentrations of these anesthetics may theoretically be above NIOSH recommendations. Using the model of a spherical shell whose radii equal the "working distance" of the anesthesiologist from the capnograph, the maximum expected exposure levels range from 802 to 100 ppm for N_2O and 11.5 to 1.4 ppm for halothane (sphere radius is 50 and 100 cm, respectively). This assumes that the sample is exhausted into a room being ventilated with 15 complete air exchanges per hour and allows for even mixing within four time constants (16 min).

To test these predictions, we used a calibrated Miran-1 Portable Infrared Gas analyzer to measure ambient levels of N_2O in an OR. An artificial lung was ventilated via an endotracheal tube, with 70% N_2O at a total gas flow of 6 L/min, delivered by an anesthesia machine previously demonstrated to be free of N_2O leaks. Sampling was done for 30 min at a distance of 50–100 cm from the exhaust port of a Puritan–Bennett capnograph connected to the endotracheal tube. Nitrous oxide levels ranged from 0 to 5 ppm before the CO_2 analyzer was turned on, and from 2 to 8 ppm while the analyzer was actively sampling, well within the error range of the equipment in use.

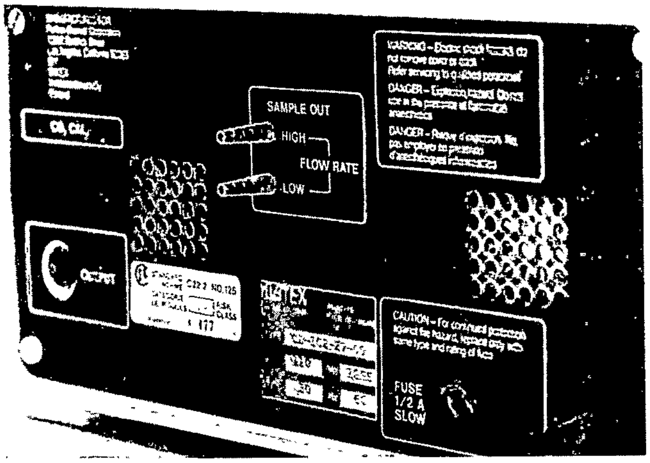

Figure 1. The rear panel of the Puritan–Bennett CO_2 analyzer. Notice the open exhaust ports for discharging the gas sample.

The disparity between calculated and measured values in the anesthesiologist's immediate working environment likely resulted from the fact that the ventilation pattern in the test OR was designed to provide high volume unidirectional flow from ceiling to floor and out. However, in those instances where ventilation is significantly lower, such capnographs may pose an underestimated pollution source. To date, there is no commercially available hardware to interface the monitors' exhaust with conventional scavenging systems. An improvised scavenging arrangement is described in the manufacturer's operation manual, but such endeavors require user modifications and entail the possibility of reducing the accuracy of the analyzer (3). Manufacturers of such devices should provide standard adaptors for use in scavenging their equipment, thereby maximizing the safety of the nearby personnel.

We would like to acknowledge the Occupational Health and Safety Branch, Division of Safety, National Institutes of Health for their invaluable assistance in taking measurements in our operating rooms.

Dan Lawson, MD
Sandra Jelenich, MD
Anesthesia Section, Clinical Center
National Institutes of Health
Bethesda, MD 20205

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Counter-irritation Reduces Pain during Cutaneous Needle Insertion

To the Editor:

Thomas (1) described a valuable method of reducing the discomfort caused by the intracutaneous injection of a local anesthetic prior to insertion of large intravenous needles or cannulas. I would like to pass along another method that can be used in addition to or in place of Dr. Thomas's method to reduce the discomfort associated with the intracutaneous injection of local anesthetic solutions.

The method involves the application of counter-irritation (CI) (2). Just before inserting the needle to inject the local anesthetic solution, the operator scratches the patient's skin near where the infiltration will be made. This can be accomplished with the extended index finger of the hand used to stretch the patient's skin. The scratching should begin one or two seconds before and continue throughout needle insertion and infiltration. Using this technique patients seldom feel the needle stick or the injection of local anesthetic. Within about 30 sec the larger intravenous needle can then be inserted without pain. Below are the results of an informal study using approximately 0.5 ml of 0.5% lidocaine and a 25-gauge needle for cutaneous infiltration with and without counter-irritation (Table 1). To determine whether they experienced discomfort during either needle insertion or infiltration, patients were asked two questions: Did you feel the needle stick? Did you feel any pain?

Table 1. Effect of Counter-irritation during Cutaneous Injection of Local Anesthetic Solution

Did you feel	With CI	Without CI
The needle?	4/25	25/25
Any pain?	3/25	21/25

Fifty patients: 25 with and 25 without CI. Numbers are "yes" responses to the questions indicated on the left. No randomization, no blinding.

Initially the operator may feel a little clumsy scratching and injecting simultaneously; however, with only a little practice one becomes quite adept. The extra effort is often amply rewarded by patients' astonishment that they have received an injection without ever feeling it. Needless to say, this method is safe and cost effective (over 1000 cases, combined operator and patient morbidity = 0, total cost = 0).

Denis L. Bourke, MD
Boston University Hospital
75 East Newton Street
Boston, MA 02118

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Vent Stitch Entrapment

To the Editor:

I read with great interest the article by Dr. Vucins et al. (Vent stitch entrapment of Swan–Ganz catheters during cardiac surgery. Anesth Analg 1984;63:772–4). Certainly they describe a very unusual situation in which the Swan–Ganz catheter was pierced by a stitch.

However, I would take issue with their statement that percutaneous removal of a suture-entrapped catheter should be avoided because of the possibility of rupture of the atrial wall with resulting pericardial tamponade or exsanguination. If a Swan–Ganz catheter is encircled by a stitch, usually the atrial wall is redundant enough in the area of stitching that bleeding is not a clinical problem if the Swan–Ganz catheter is removed percutaneously by sliding it through the loop. Certainly if continuity of the stitch is disrupted (as would have to be the case if a stitch passed through the Swan–Ganz catheter), the chances of bleeding would be greater. But even in the case described a clot had formed outside the atrial wall, avoiding bleeding.

One would like, if possible, to avoid reoperation in any patient that has undergone cardiac surgery. Since an earlier report (1), we have had two more situations in which a Swan–Ganz catheter was easily removed by slipping it through an encircling atrial suture. In each case it was done percutaneously without any sequelae—thereby avoiding reoperation.

If the Swan–Ganz catheter does not move easily, then the possibility of a perforating suture should be raised and excess traction must be avoided. However, if the Swan–Ganz line moves easily through the suture loop, indicating that there is probably an encircling atrial suture, percutaneous removal is usually easily performed at low risk.

Peter C. Block, MD
Harvard Medical School
Cardiac Catheterization Laboratory
Bullfinch One
Massachusetts General Hospital
Boston, MA 02114

Reference

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Narcotics and the Sphincter of Oddi

To the Editor:

The study of McCammon et al. (1) on the effects of narcotic analgesics and antagonists–agonists on biliary tree dynamics is the first study of the latter group of drugs in this area in humans. I would like to comment on some limitations in the design of this and previous observations utilizing similar methods.

This study does not address the problem of uneven patient distribution with regard to duration and extent of biliary tract disease. Cholangitis and pericholangitis ultimately result in fibrotic changes in the wall of the common bile duct, resulting in stricture and sclerosis together with decreased motility of the sphincter of Oddi, making it unable to respond to the spasmogenic effect of the narcotic. This may be a possible explanation for the unpredictability of narcotic-elicited spasm noted by McCammon et al. One should not expect the same responses (spasm) in patients with a one-month history of biliary disease and in patients with long-standing disease. The location and type of biliary tract stones (in the gallbladder or in the common duct, single large calculus or multiple small stones, etc.) are equally important. Furthermore, surgical technique may influence the response of the biliary tract to narcotics: a prolonged and technically difficult biliary tract operation causing significant degree of operative injury to the common duct and neighboring structures may introduce unpredictable factors into the narcotic-sphincter interaction. Measurements made after cholecystectomy, without choledochostomy, as was the case in their study, may not be comparable to those made after exploration of the common bile duct.

As evidenced by their citation of a previous study (2), the authors are aware of the importance of temperature of the contrast material in determining the response of the sphincter of Oddi. Temperature of the contrast media was not reported in this study, thus another possible variable was introduced.

Even if these questions are answered, the clinical applicability of the study remains in doubt. The degree of obstruction to the common duct flow produced by pathologic conditions (e.g., fibrotic stricture or impacted stone) is not compared to the degree of obstruction produced by narcotic-induced spasm. The highest mean intrabiliary tract pressure found by the authors, 17.5 cm of saline, was with fentanyl. This produced only a 35% decrease in 60-sec flow rate. Would this mild degree of spasm interfere with intraoperative cholangiography? A surgeon's thumb on a syringe loaded with contrast media exerts far greater pressure!

The authors themselves provide evidence that factors other than narcotics must be considered when assessing common duct patency. They excluded 9 out of 65 patients because of unexplained increases in intrabiliary pressure between control measurements, prior to the administration of any narcotic. Would these occurrences have been attributed to narcotics had these patients been included in the study? Indisputable statistical evidence of one agent's superiority is obvious from the results presented. Yet in the light of the problems mentioned, the clinical relevance remains questionable and further well-controlled studies of this important interaction are more than warranted.

Jan Karasek, MD
Department of Anesthesiology
SUNY Upstate Medical Center
750 East Adams Street
Syracuse, NY

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In Response:

We welcome the opportunity to respond to Dr. Karasek's Letter to the Editor. Dr. Karasek correctly notes that the duration or extent of biliary tract disease was not known in our patients. We would argue however that this is rarely, if ever, known. Likewise Dr. Karasek correctly states that cholangitis and pericholangitis can result in fibrotic changes in the sphincter of Oddi and, therefore, decreased motility of the sphincter of Oddi. If significant stricture of the sphincter of Oddi had been present, one would expect abnormally high pressures and low flows. We did not note this in our patients. In fact, the flow and pressure measurements were comparable to those in the study of White et al. (1). We are, however, presently completing a larger study of patients with biliary tract disease, which will allow comparison of manometric measurements and sphincter of Oddi pathology (biopsy findings).

We also agree that manometric measurements made after cholecystectomy without any additional biliary tract exploration are not comparable to manometric measurements made after exploration of the common duct. Indeed, it is well accepted that prior surgical manipulation of the sphincter of Oddi can result in spasm. We purposefully did not explore the common duct, utilized saline (room temperature), and excluded patients from the study if there was a greater than 10% change between the first and second set of measurements. We felt that this gave us the best chance to evaluate, in vivo, the relative spasmogenic effects of narcotic analgesics and the agonists–antagonists.

The final question raised is would this mild degree of spasm interfere with intraoperative cholangiography? The study by Jones et al. (2) indicates that at least with fentanyl-supplemented anesthesia, failure of passage of contrast media is uncommon (3%). Additionally, other reports in the literature attest to the fact that other narcotics may cause spasm of the sphincter of Oddi and abnormal cholangiograms (3,4). Although the incidence of abnormal cholangiography secondary to narcotic-induced spasm may be low, it is valuable for the practicing anesthesiologist to be aware that the analgesics vary in their spasmogenic potential. Clinically, a narcotic as part of the premedicant regimen is questionable in a patient with known biliary tract disease. Based on our data, if an analgesic is considered desirable, perhaps one of the newer agonists–antagonists would be preferable. Likewise, patients with biliary tract disease may require a balanced anesthetic technique for reasons of hemodynamic stability. Here again, the possibility of narcotic-induced spasm must be appreciated if needless common duct exploration is to be avoided.

R.L. McCammon
R.K. Stoelting
J.A. Madura
Indiana University
School of Medicine
1120 South Drive
Indianapolis, IN 46223

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Importance of Anesthetic Equivalence

To the Editor:

One important factor that evidently has not been considered in the otherwise excellent clinical study by Bastard et al.,* in their comparison of the circulatory effects of halothane and isoflurane (1), was the lack of anesthetic equivalence between halothane and isoflurane. According to previously published results (2–4), with a little extrapolation, the MAC of 50% N_2O–halothane in 56-yr-old patients should be 0.39% and MAC of 50% N_2O–isoflurane should be 0.59%. Consequently, the patients in Bastard's study received 1.8 × MAC halothane and 1.4–1.5 × MAC isoflurane. It is certainly conceivable that equianesthetic concentrations of isoflurane may have produced different results from those reported. At the very least, this difference needs to be noted.

Robert G. Merin, MD
Department of Anesthesiology
University of Texas Health Sciences Center
at Houston
Houston, TX 77030

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2. Saidman LJ, Eger EI. Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 1964;25:302–6.
3. Gregory GA, Eger EI, Munson ES. The relationship between age and halothane requirement in man. Anesthesiology 1969;30:488–91.
4. Stevens WC, Dolan WM, Gibbons RT, et al. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 1975;42:197–200.

In Response:

We are grateful for the opportunity to reply to Dr. Merin's letter on the subject of anesthetic equivalence, which is so germaine to a comparison of the hemodynamic effects of isoflurane (I) and halothane (H). However, we cannot agree with Dr. Merin's calculation of MAC equivalents. The effect of N_2O on the reduction of MAC for a volatile agent is arithmetic, not geometric. Table 1 shows how MAC values were calculated in our study.

Table 1. Calculation of MAC Values

	Anesthesia		Surgery	
	Isoflurane	Halothane	Isoflurane	Halothane
MAC in O_2 (End-tidal conc. vol. %)	1.15	0.75	1.15	0.75
Anesthetic concentration (End-tidal conc. vol. %)	0.84	0.71	0.91	0.71
MAC equivalent	0.73	0.94	0.79	0.94
MAC equivalent of 50% N_2O	0.5	0.5	0.5	0.5
Total MAC	1.23	1.44	1.29	1.44

The difference in MAC values between the groups is small. It arose during the conduct of the study because the anesthetic concentration was reduced in patients whose systolic blood pressures decreased below 100 mm Hg: this occurred more frequently in the I group during anesthesia before the start of surgery. Thus we cannot disagree with Dr. Merin: if both groups had received equivalent concentrations of agents, the difference in blood pressure between the groups during "anesthesia" might have achieved statistical significance. We have no reason to suppose that there would have been any other significant differences.

Oliver G. Bastard, FFARCS*
John R. Moyers, MD
James G. Carter, MD
Regional Cardiothoracic Centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne, NE7 7DN

Avoiding Air Infusion with Pressurized Infusion Systems: A New Hazard

To the Editor:

Since publication of our recent article (1), we have uncovered a new hazard associated with pressurized infusion systems. This issue affects not only our system, but also any infusion system, manual or mechanized, that can deliver volume at high pressure as the fluid bag is emptying.

Travenol recently increased the air in their 1-L fluid bags from approximately 35 to 70 ml (personal communication, M.S. Goldstein, MD, Medical Director, Travenol Laboratories). We have contacted Travenol and informed them of the increased hazard of air embolism caused by their product change; they are evaluating possible courses of action. To decrease the potential danger now, we suggest that the air be eliminated from each bag before use. Another possible safeguard is the use of intravenous tubings with large volumes, including drip chamber or hand pump. A 2-m wide-bore Y-type set with large filter (4C2194, Travenol, Oak Park, IL), which we used in our study, has a drip chamber volume of approximately 47 ml and a total tubing volume of 72 ml when pressurized to 300 mm Hg, if it is filled according to manufacturer's instructions. There is usually enough volume in the tubing to contain air emptying from the fluid bag, without passing it on to the patient. On the other hand, a simple 1.8-m intravenous tubing (2C0001, Travenol) has a drip chamber volume of approximately 10 ml and total tubing volume of 20 ml. Use of a smaller-volume intravenous tubing does permit air to escape, which could endanger the patient.

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*Editor's note: Since publication of the original article, the author's name has been changed to O. G. W. Weldon. This material will be indexed under both names.

The possibility of air infusion exists with every pressurized infusion system. Users should be aware of the recently increased danger associated with 1-L Travenol bags.

Beverly K. Philip, MD
James H. Philip, MD
Bioengineering Laboratory
Department of Anesthesia
Brigham and Women's Hospital
Harvard Medical School
Boston, MA 02115

Reference

1. Philip JH, Philip BK. Pressurized infusion system for fluid resuscitation. Anesth Analg 1984;63:779–81.

Book Reviews

5-Hydroxytryptamine in Peripheral Reactions

Fred DeClark, Paul M. Vanhoutte, eds. New York: Raven Press, 1982, 230 pp, $37.00.

This volume is the result of a workshop, "5-Hydroxytryptamine in Peripheral Reactions," held by leading scientists in the field. It summarizes our current understanding of the role of 5-hydroxytryptamine in both normal and pathologic states of peripheral organs.

The work is conveniently divided into four sections. The first summarizes the sites of production, storage, and release of 5-hydroxytryptamine; its transport and release by platelets; and its subsequent metabolism by vascular endothelial cells. The second section describes both the direct physiologic effects of 5-hydroxytryptamine as well as serotonogenic amplifying mechanisms in the intact organism, blood vessel wall and platelets. Two papers summarize the physiologic effects of prostacyclin for comparison. A subsequent section focuses on pathologic states in which 5-hydroxytryptamine may play an important role. These include malignant hyperthermia, Duchenne's muscular dystrophy, shock, and hypertension. Finally, the pharmacologic profile of ketanserin, a 5-HT$_2$ specific serotonogenic receptor antagonist, is presented. As this drug is devoid of agonist properties, it has assumed an important role in elucidating the role of 5-hydroxytryptamine in both normal and pathologic conditions.

Although each paper is in and of itself an independent work, this style of organization of the papers provides for a clear and logical format of presentation. The papers are well written, quite readable, and possess ample references. Although the first sections are of interest primarily to pharmacologists and physiologists, the later sections are of interest to clinicians who manage patients with cardiovascular disease, hypertension, and muscular dystrophies. The papers discuss the role of 5-hydroxytryptamine in these pathologic conditions and the possible therapeutic potential of ketanserin.

James K. Alifimoff, MD
Instructor of Anesthesiology
University of Pittsburgh School of Medicine
Pittsburgh, PA 15213

Atlas of Emergency Medicine, 2nd ed.

Peter Rosen, George L. Sternbach, eds. Baltimore: Williams and Wilkins Company, 1983, 234 pp, $34.00.

Emergency physicians are called on daily to perform a variety of procedures. A good reference text on procedures must be an essential part of their library. *Atlas of Emergency Medicine* is one of many texts that attempt to address that need. The procedures are grouped according to organ system and the material is clearly written with easily readable print. Large, clearly drawn illustrations are another of its strengths; however, its organization is questionable in several respects. Background and indications for each procedure are discussed but are physically separate from instruction on performance of each procedure or technique. This is awkward, forcing the reader to flip back and forth anywhere from a few to a dozen or more pages. Also, the authors do not provide a list of required instruments and materials for each procedure. The reader must search through the text for this information.

A detailed discussion of indications, precise instructions, and technical pearls are all part of a really good procedures book. Unfortunately, the instruction provided in this text is lacking in these areas. Cricothyrostomy is described as the "procedure of choice when it is indicated," but the indications are never discussed. Percutaneous needle cricothyrostomy is recommended "under appropriate circumstances," but the circumstances are never discussed. Also, for needle cricothyrostomy, neither the appropriate size catheter nor the volume and flow of oxygen required are specified. No time limit is given for endotracheal intubation attempts or for endotracheal suctioning and the section on cardiac wound repair is only three sentences long. Nowhere is the dearth of material more apparent than in the section on intradermal suturing, where we are told to swathe the child in sheets, irrigate the wound, anesthetize the wound, and place subcutaneous sutures, all without any further discussion of how.

In general, this text does not attempt to address the special considerations of the pediatric patient. Occasional advice is given but another text would be required to adequately cover this area. Finally, although a number of controversial areas are touched on, the text is unfortunately without references.

A good procedures book requires much of its author. A detailed treatment of indications, contraindications, techniques, and alternate techniques is an exhausting task. However well intentioned the authors were, this book fails to provide these things and thus falls short of sound instruction on emergency medical procedures.

W. Marc Barnett, MD
Department of Emergency Medicine
East Liverpool City Hospital
East Liverpool, Ohio

Books Received

Basic and Clinical Pharmacology (2nd Edition). BG Katzung. Los Altos, CA: Lange Medical Publications, 1984, 888 pp, $26.00.

The Pathway for Oxygen. ER Weibel. Cambridge, MA: Harvard University Press, 1984, 425 pp, $27.50, (paper) $17.50.

Plexus Anesthesia (Perivascular Techniques of Brachial Plexus Block). AP Winnie. Philadelphia: WB Saunders Company, 1983, 272 pp.

Understanding Anesthesia Equipment, Construction, Care and Complications (2nd Edition). JA Dorsch, SE Dorsch. Baltimore: Williams and Wilkins, 1984, 458 pp, $47.00.

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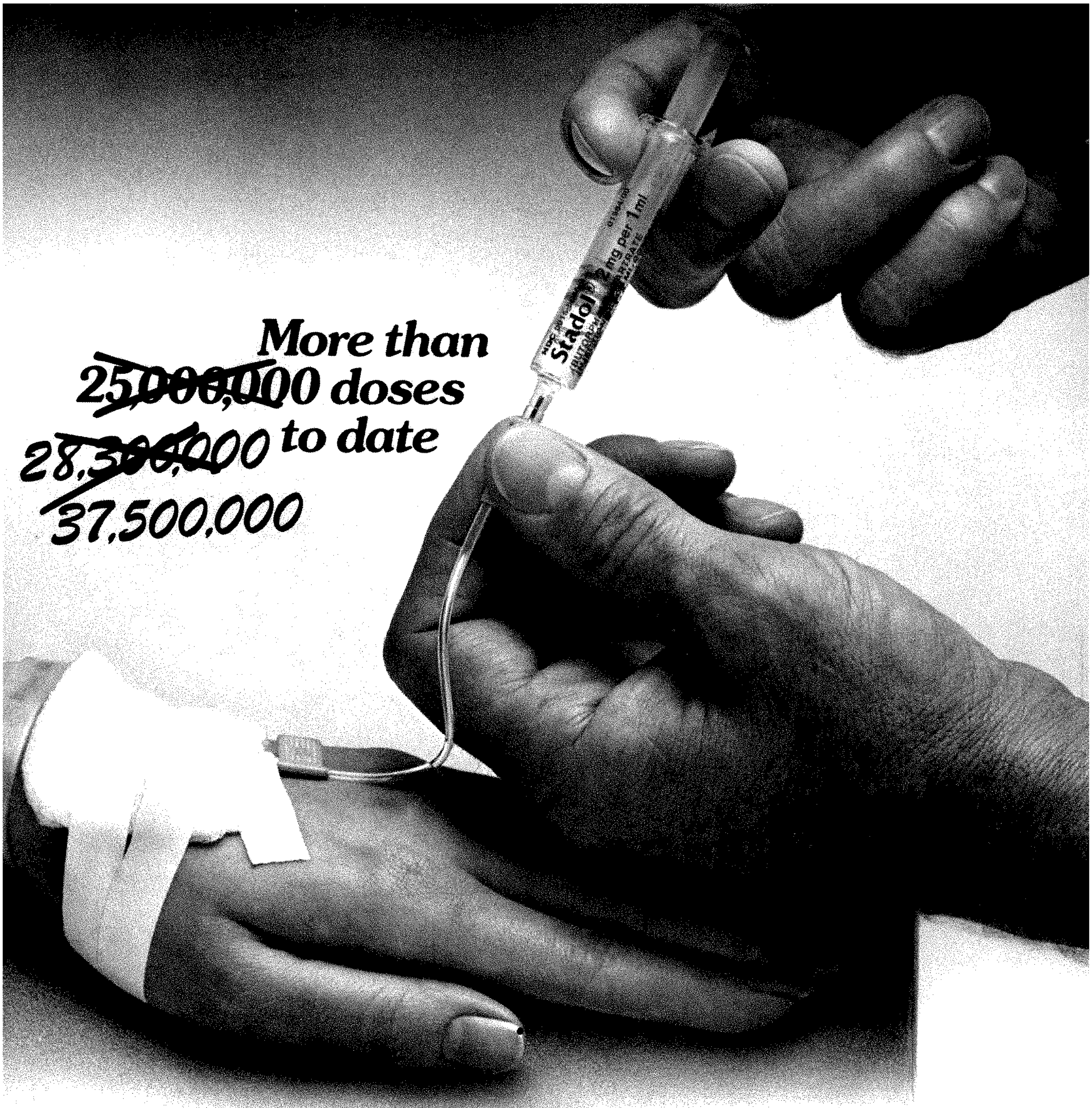

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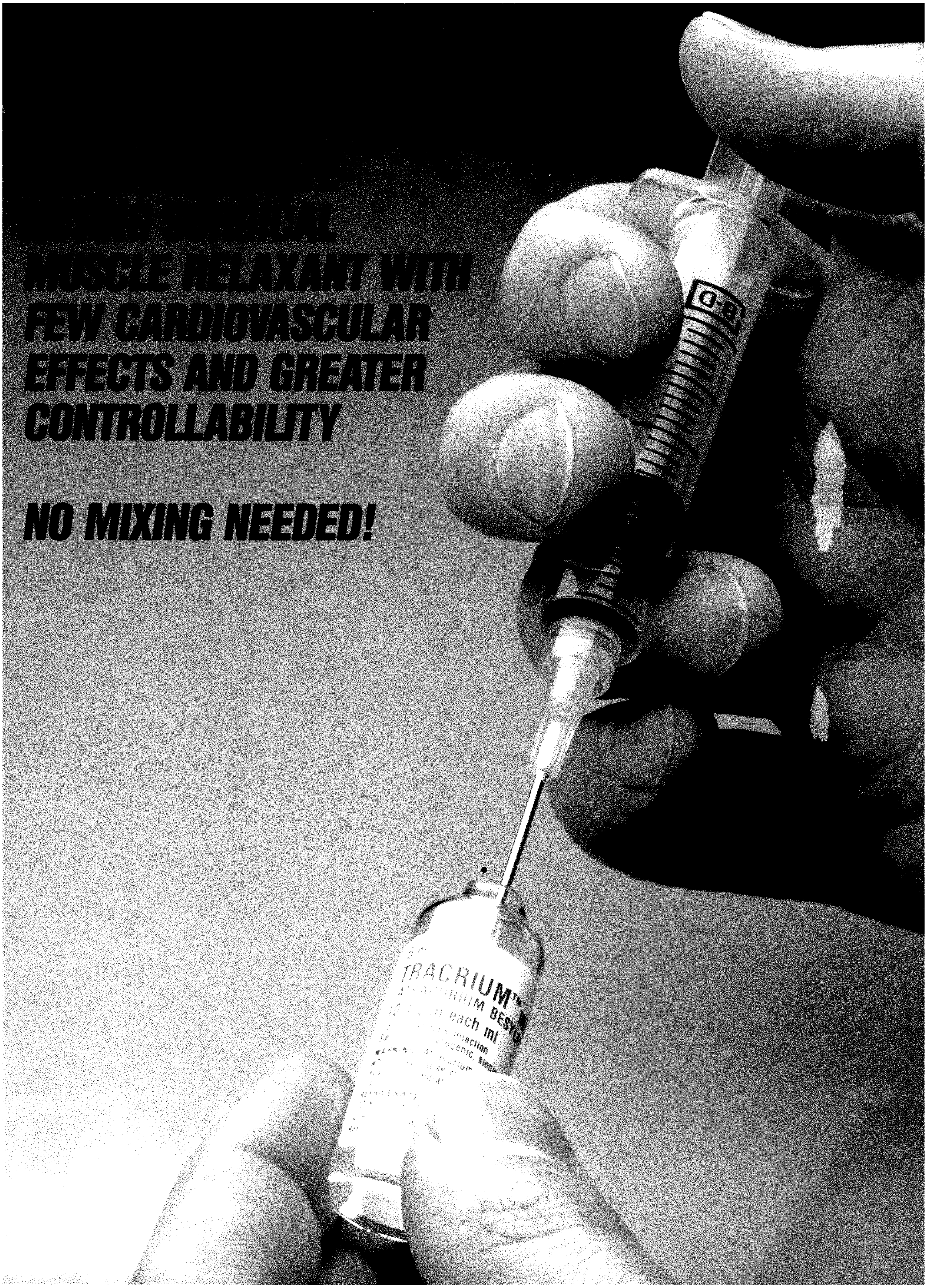
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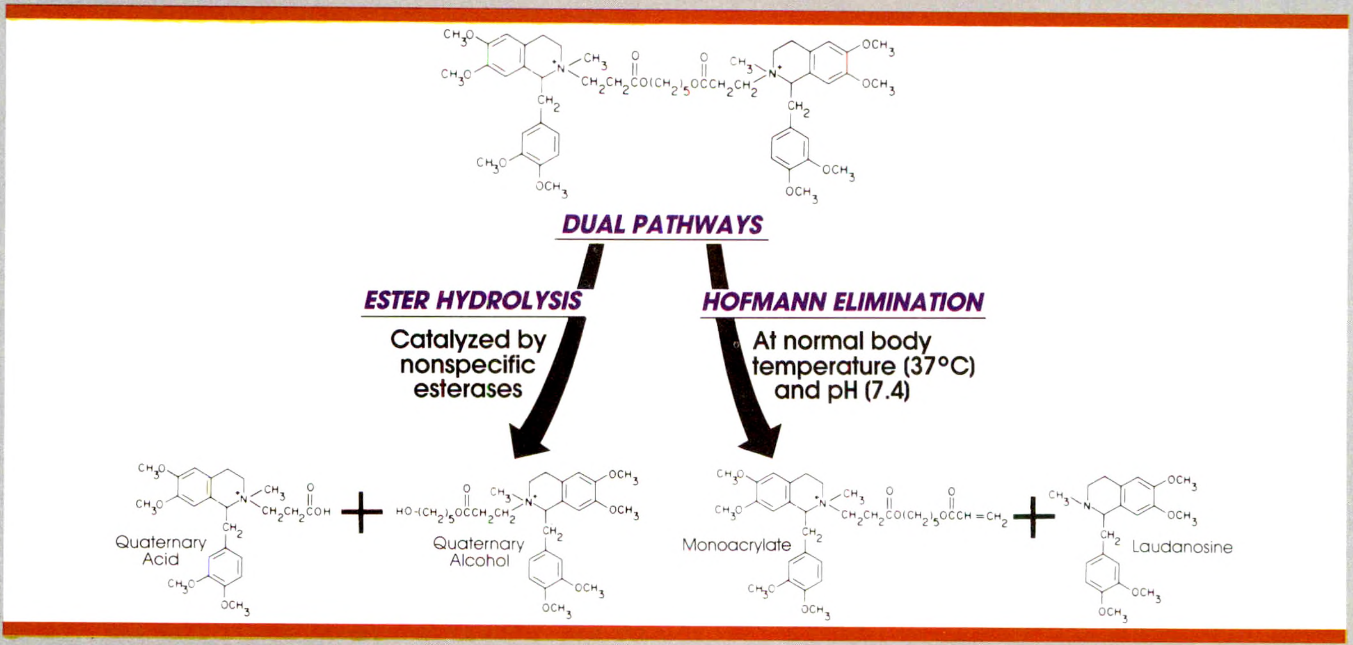

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These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

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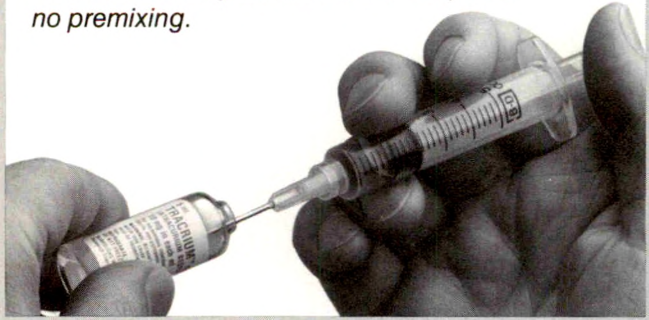

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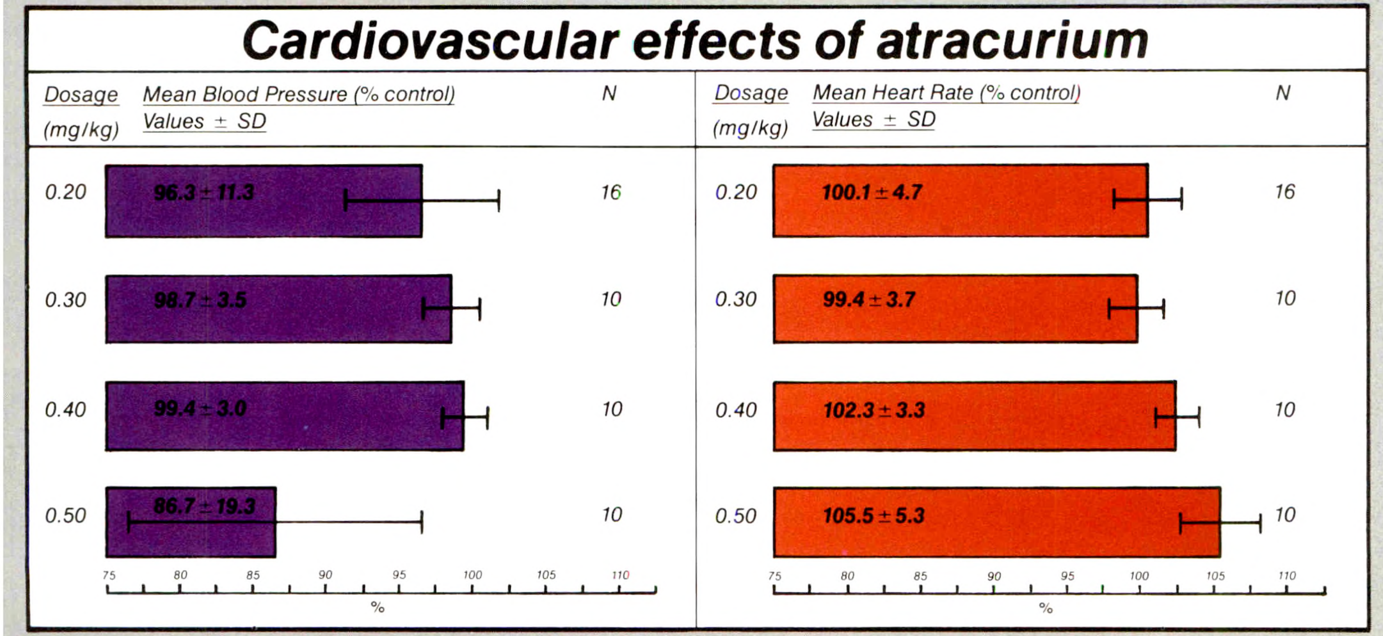

Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ *Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

☐ *Once recovery begins, it is relatively rapid and independent of dose*

☐ *This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

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☐ *Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

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☐ *The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.

TRACRIUM® INJECTION
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TRACRIUM® INJECTION
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DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

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Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).
Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

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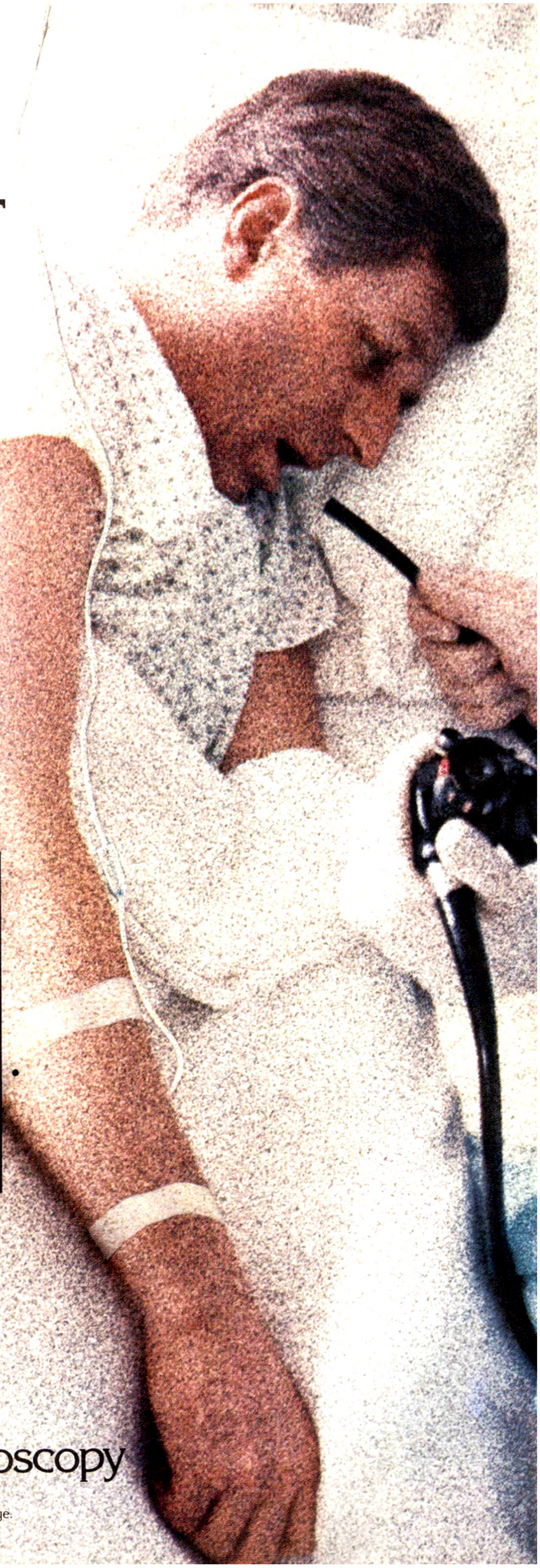

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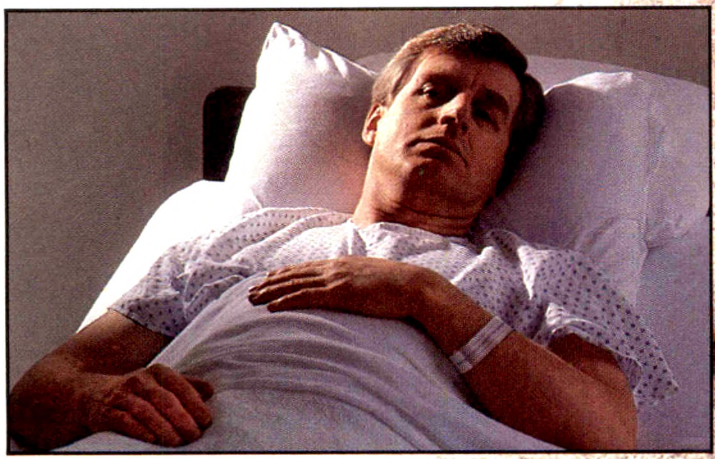

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In the moments before endoscopy

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References: 1. Diazepam and lorazepam in anesthesia. *Drug Ther Bull 17*(5): 19-20, Mar 2, 1979. **2.** Conner JT, *et al: J Clin Pharmacol 18*:285-292, May-Jun 1978. **3.** George KA, Dundee JW: *Br J Clin Pharmacol 4*:45-50, Feb 1977. **4.** Dundee JW, Pandit SK: *Br J Pharmacol 44*:140-144, Jan 1972. **5.** Dundee JW, *et al: Br J Anaesth 51*:439-446, May 1979. **6.** Gregg JM, Ryan DE, Levin KH: *J Oral Surg 32*:651-664, Sep 1974.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.,* operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.,* phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use

Injectable Valium® (diazepam/Roche)

topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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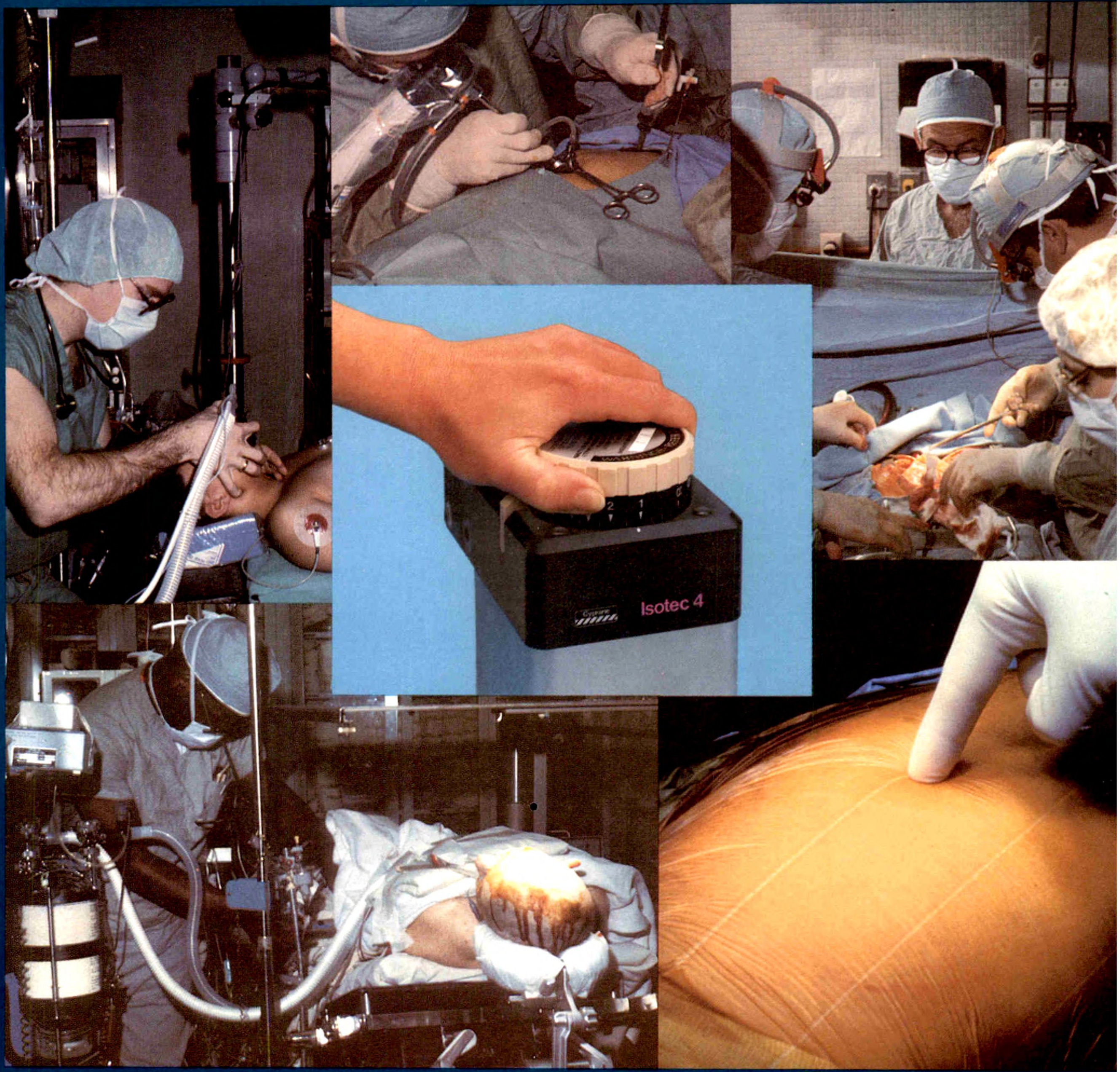

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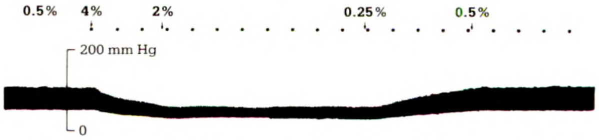
A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

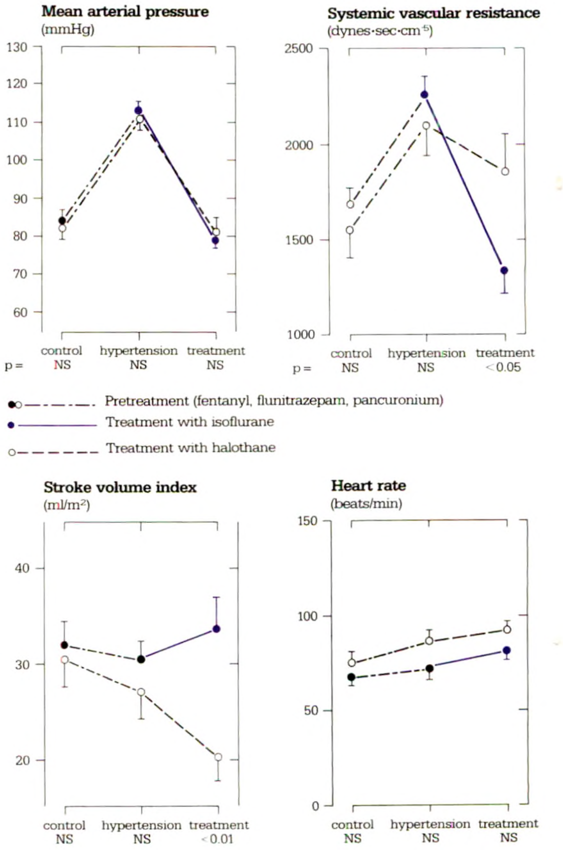
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surger (Adapted from Hess et al[3]).



Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)

Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8] *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983. 2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981. 7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

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(isoflurane)

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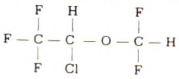
(isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$F-\underset{F}{\overset{F}{C}}-\underset{Cl}{\overset{H}{C}}-O-\underset{F}{\overset{F}{C}}-H$$

Some physical constants are:

Molecular weight		184.5
Boiling point 760 mm Hg		48.5 °C (Uncorr.)
Refractive index n_D^{20}		1.2990—1.3005
Specific gravity 25°/25 °C		1.496
Vapor pressure in mm Hg.**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T}$$

where:
A = 8.056
B = −1664.58
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37 °C	
Water/gas	0.61
Blood/gas/gas	1.43
Oil/gas	90.8
Partition coefficients @ 25 °C—rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9 %
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitorus oxide at 900 joules/sec and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anaesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

Age	100 % Oxygen	70 % N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administerd epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known senitivity to FORANE (isoflurane) or other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesi There may be a transient rise in cerebral spinal fluid pressure which is fully reversible wi hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) shou only be administered in an adequately equipped anesthetizing enivronment by those who a familiar with the pharmacology of the drug and qualified by training and experience to manag the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a sligl decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetic small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinin with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxant most notably nondepolarizing muscle relaxants, and M.A.C. (minimum alveolar concentratio is reduced by concomitant administration of N_2O. See Clinical Pharmacology.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposur might induce neoplasia. Isoflurane was given at ½, ⅛, and 1/32 M.A.C. for four in-utero exposure and for 24 exposures to the pups during the first nine weeks of life. The mice were killed a 15 months of age. The incidence of tumors in these mice was the same as in untreated contr mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have possible anesthetic-related fetotoxi effect in mice when given in doses 6 times the human dose. There are no adequate and wel controlled studies in pregnant women. Isoflurane should be used during pregnancy only if th potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because man drugs are excreted in human milk, caution should be exercised when isoflurane is administere to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrom known as malignant hyperthermia. The syndrome includes nonspecific features such as muscl rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It shoul also be noted that many of these nonspecific signs may appear with light anesthesia, acut hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperatur (which may rise rapidly early or late in the case, but usually is not the first sign of augmente metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 an pH may decrease, and hyperkalemia and a base deficit may appear. Treatment include discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene and application of supportive therapy. Such therapy includes vigorous efforts to restore bod temperature to normal, respiratory and circulatory support as indicated, and management o electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodiu intravenous for additional information on patient management.) Renal failure may appear later and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting, and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\%\ \text{isoflurane} = \frac{100\,P_V F_V}{F_T(P_A - P_V)}$$

where P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (ml)
F_T = Total gas flow (ml)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbituate. Inspired concentrations of 1.5 to 3% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia my be sustained with a 1.0-2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5% to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

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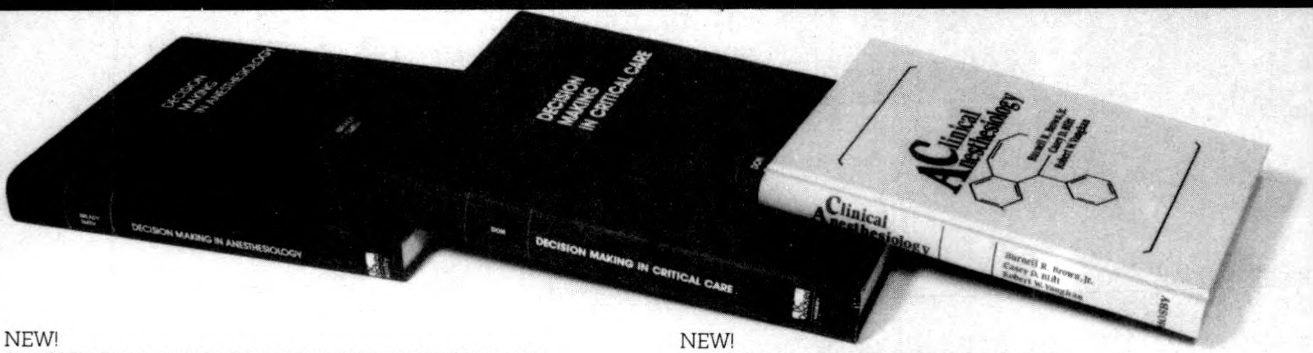

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March, 1985. Approx. 250 pages, with illustrations. (B-1047-8) Mosby distributes this Blackwell Scientific Publication. About $32.50.

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This course will review physiology, pharmacology, and anesthetic responses unique to the pediatric patient. Our featured guest speaker is *Dr. D. Ryan Cook*, Professor and Chief of Anesthesiology, Children's Hospital of Pittsburg, who will discuss neonatal anesthesia, muscle relaxants and neuromuscular disease, and liver transplantation.

Other topics include congenital heart disease, anesthetic equipment and mishaps, recovery room problems, resuscitation, management of burns, a panel on lung development, control of respiration, and prematurity; a second panel will cover new muscle relaxants, pharmacokinetics of muscle relaxants, and neuromuscular disease. The luncheon meeting includes an open discussion of problem cases. Further topics include outpatient anesthesia, premedication, retinopathy of the premature infant, and pediatric pharmacology.

Three half-day sessions are approved for 15 credit hours in Category 1 of the Physician's Recognition Award of the AMA. Application has been submitted to the American Association of Nurse Anesthetists for continuing education credits to be awarded to nurse anesthetists completing this course.

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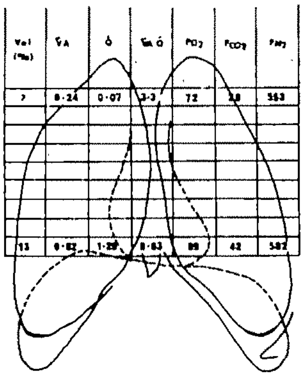
Course Directors: Drs. John F. Ryan and Charles J. Coté, Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts.



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ABSTRACTS

An important part of this symposium will be poster presentation of original papers. Abstracts not exceeding 500 words are invited with emphasis on the following subjects:

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High frequency ventilation; Resuscitation; Monitoring advances;
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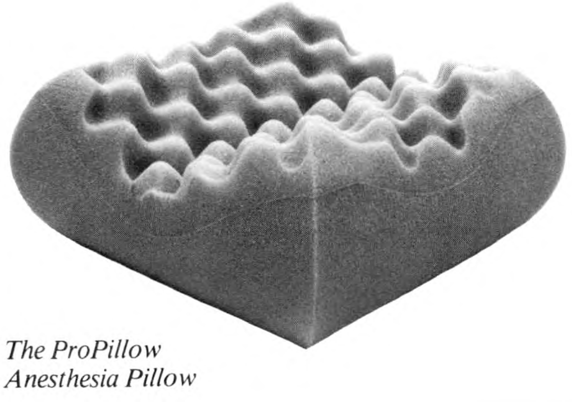

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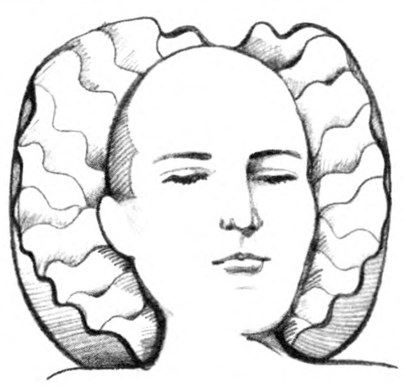

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When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED—Regonol is available in:
5 mg./ml.: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

REFERENCES:

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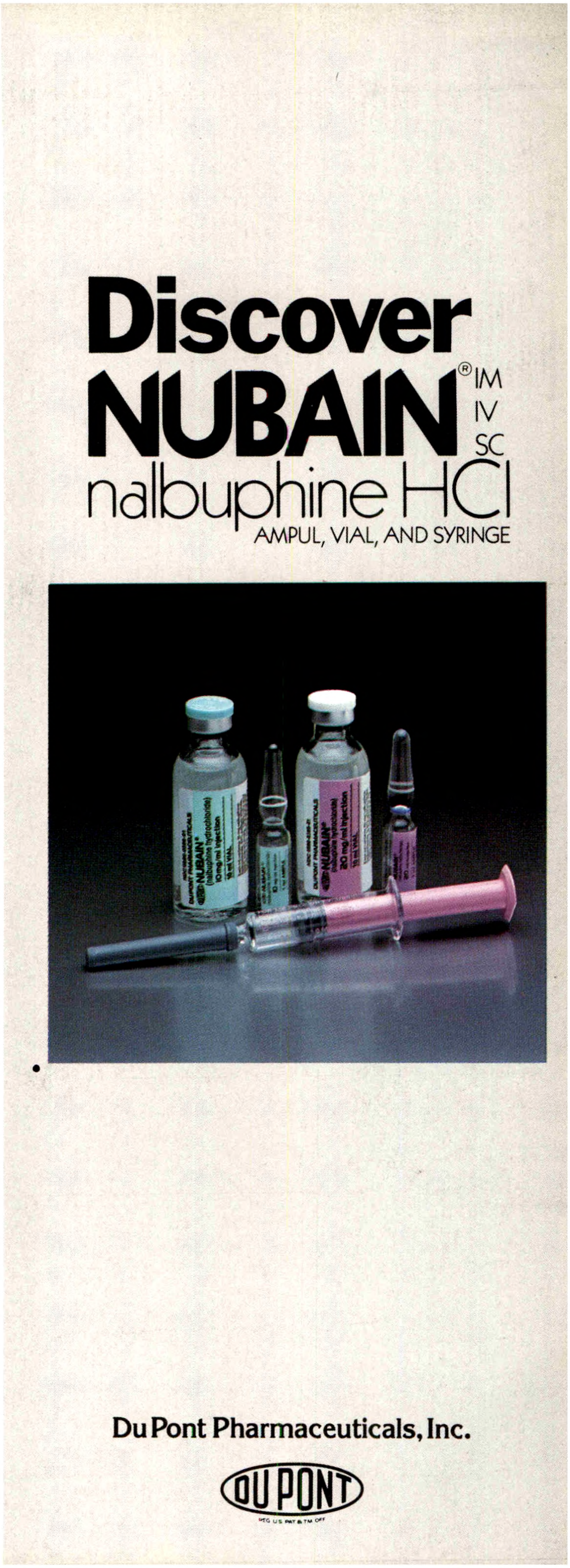

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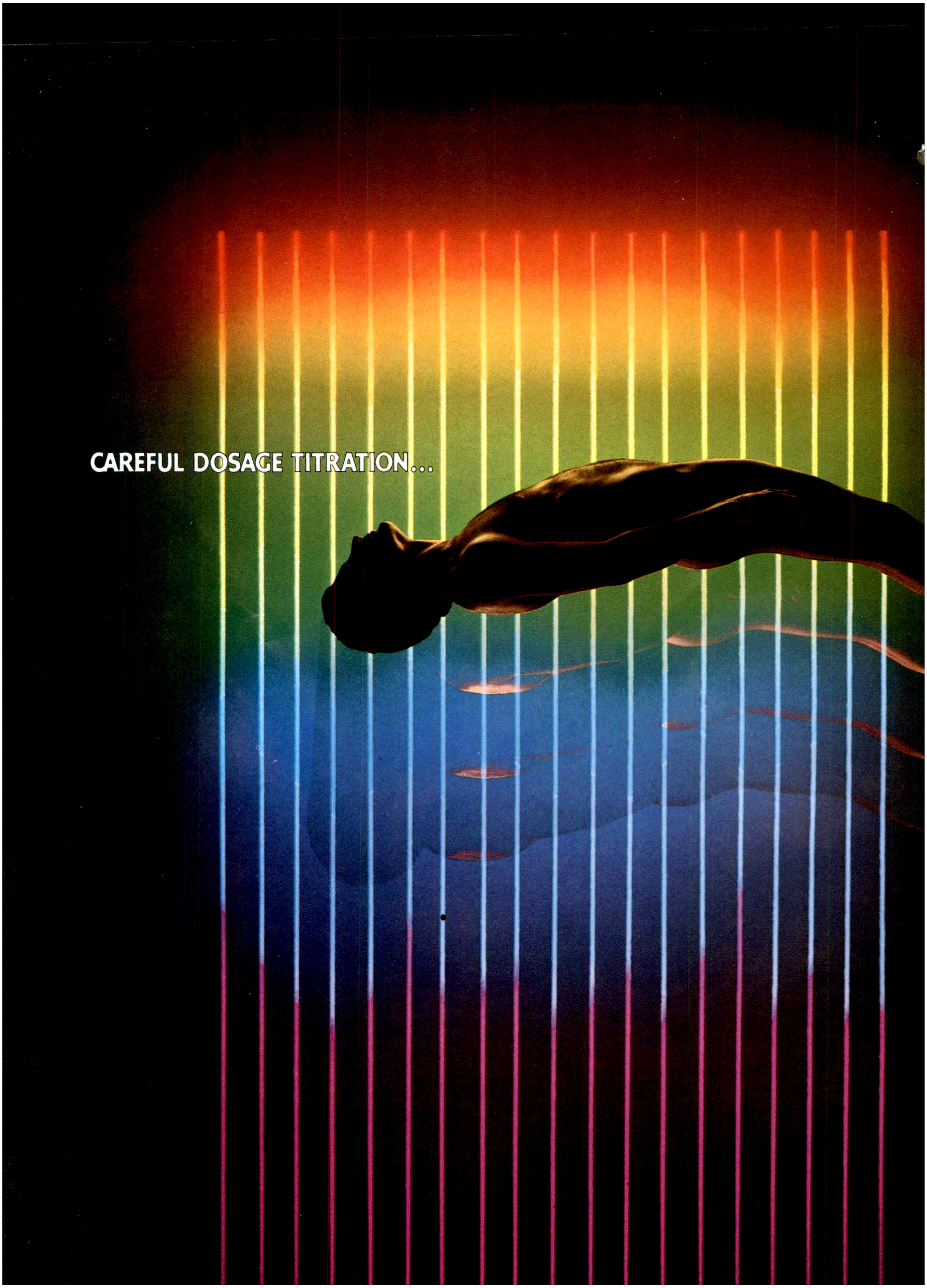
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INDICATIONS AND USAGE NARCAN is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and the narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected acute opioid overdosage.

CONTRAINDICATIONS NARCAN is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs.

PRECAUTIONS In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity and mutagenicity studies have not been performed with NARCAN. Reproductive studies in mice and rats demonstrated no impairment of fertility.

Use in Pregnancy: Pregnancy Category B: Reproduction studies performed in mice and rats at doses up to 1,000 times the human dose, revealed no evidence of impaired fertility or harm to the fetus due to NARCAN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

ADVERSE REACTIONS Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of NARCAN may result in significant reversal of analgesia, and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of NARCAN postoperatively (see PRECAUTIONS & USAGE IN ADULTS—POSTOPERATIVE NARCOTIC DEPRESSION). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

OVERDOSAGE There is no clinical experience with NARCAN overdosage in humans.

In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injection: no toxic effects were seen at 10 mg/kg/day for 3 weeks.

DOSAGE AND ADMINISTRATION NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN the patient should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of NARCAN in 500 ml of either solution provides a concentration of 0.004 mg/ml. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of narcotic induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one or two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Narcotic Depression Follow the recommendations and cautions under **Adult Postoperative Depression**. For the initial reversal of respiratory depression NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two to three minute intervals to the desired degree of reversal.

USAGE IN NEONATES Narcotic-Induced Depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M., or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

HOW SUPPLIED—NARCAN (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration is available as:

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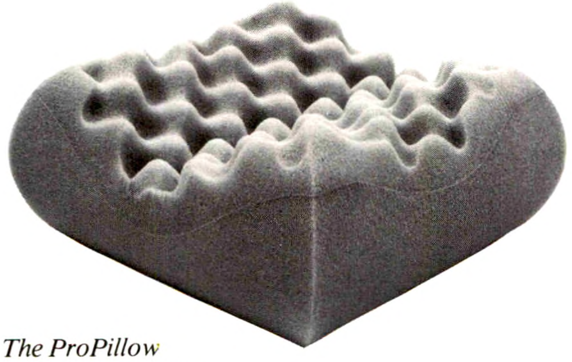

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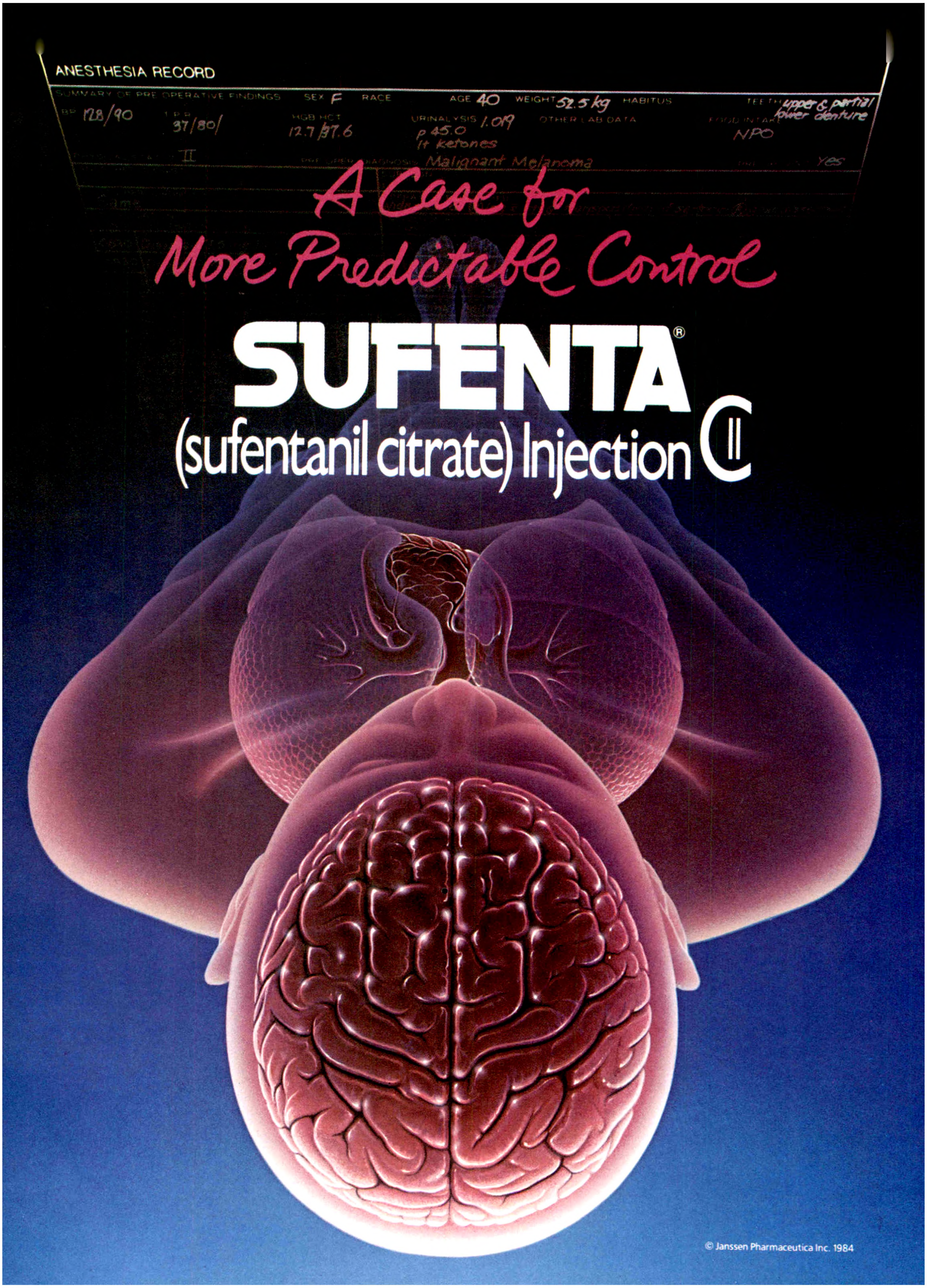

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II PRE OPER DIAGNOSIS Malignant Melanoma YES

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1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.
4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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SUFENTA®

(sufentanil citrate) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be $\frac{1}{5}$-$\frac{1}{7}$ those of fentanyl on a mg/kg basis.) At doses of up to 8 μg/kg, SUFENTA provides profound analgesia; at doses ≥8 μg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 μg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 μg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 μg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 μg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 μg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 μg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 μg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 μg/kg in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to $\frac{1}{4}$ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:
Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 μg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 μg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 μg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 μg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
1-2 μg/kg: administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 μg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
2-8 μg/kg: administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
8-30 μg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 μg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 μg/kg, catecholamine release is attenuated. Dosages of 25-30 μg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

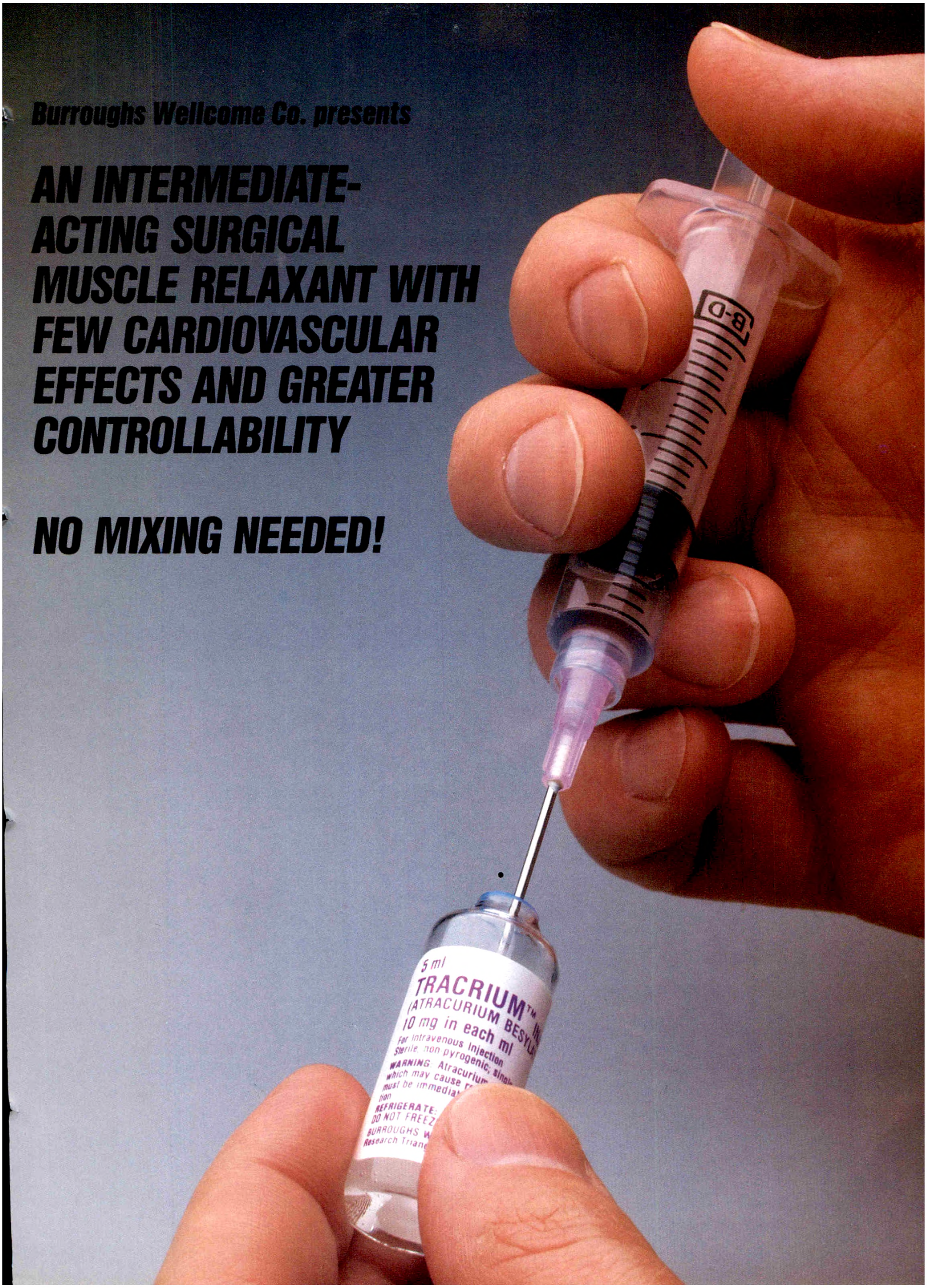
NDC 50458-050-01	50 μg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 μg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 μg/ml, 5 ml ampoules in packages of 10

Protect from light. Store at room temperature.

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854

7618500

U.S. Patent No. 3,998,834
May 1984


Burroughs Wellcome Co. presents
AN INTERMEDIATE-ACTING SURGICAL MUSCLE RELAXANT WITH FEW CARDIOVASCULAR EFFECTS AND GREATER CONTROLLABILITY
NO MIXING NEEDED!
B-D
5 ml
TRACRIUM™
(ATRACURIUM BESYLATE
10 mg in each ml
For intravenous injection
Sterile, non pyrogenic
REFRIGERATE
DO NOT FREEZE
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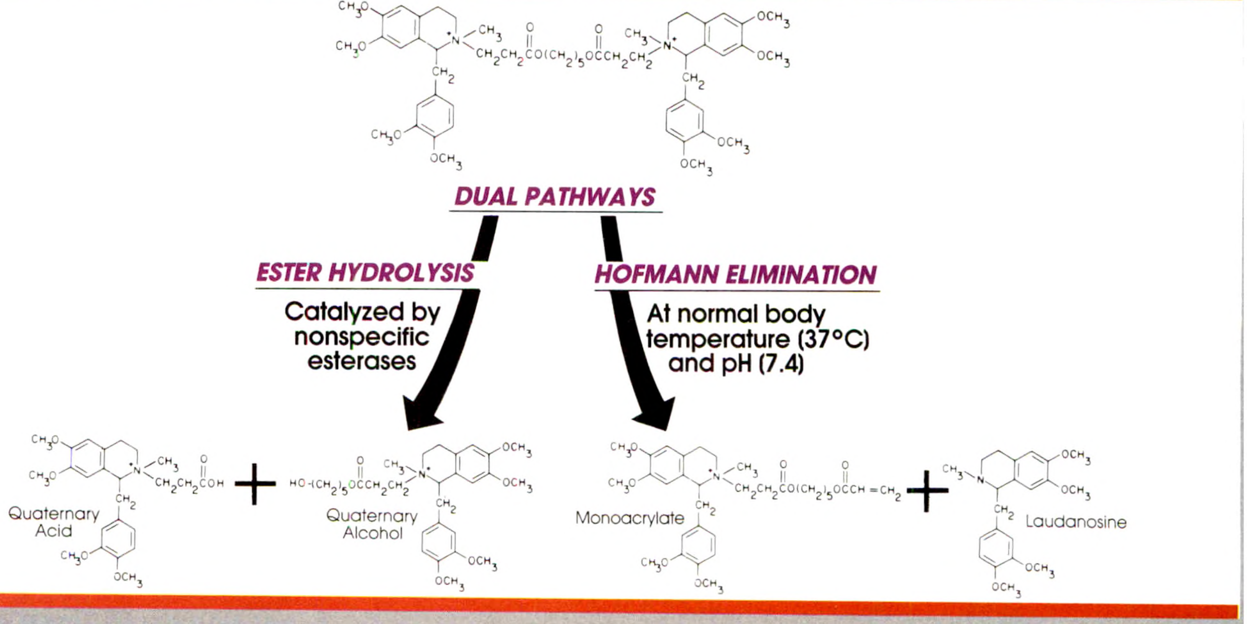
UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

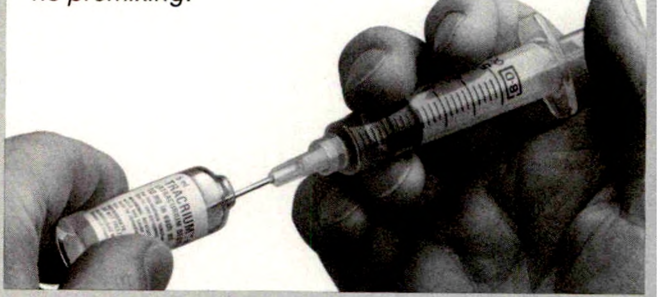
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

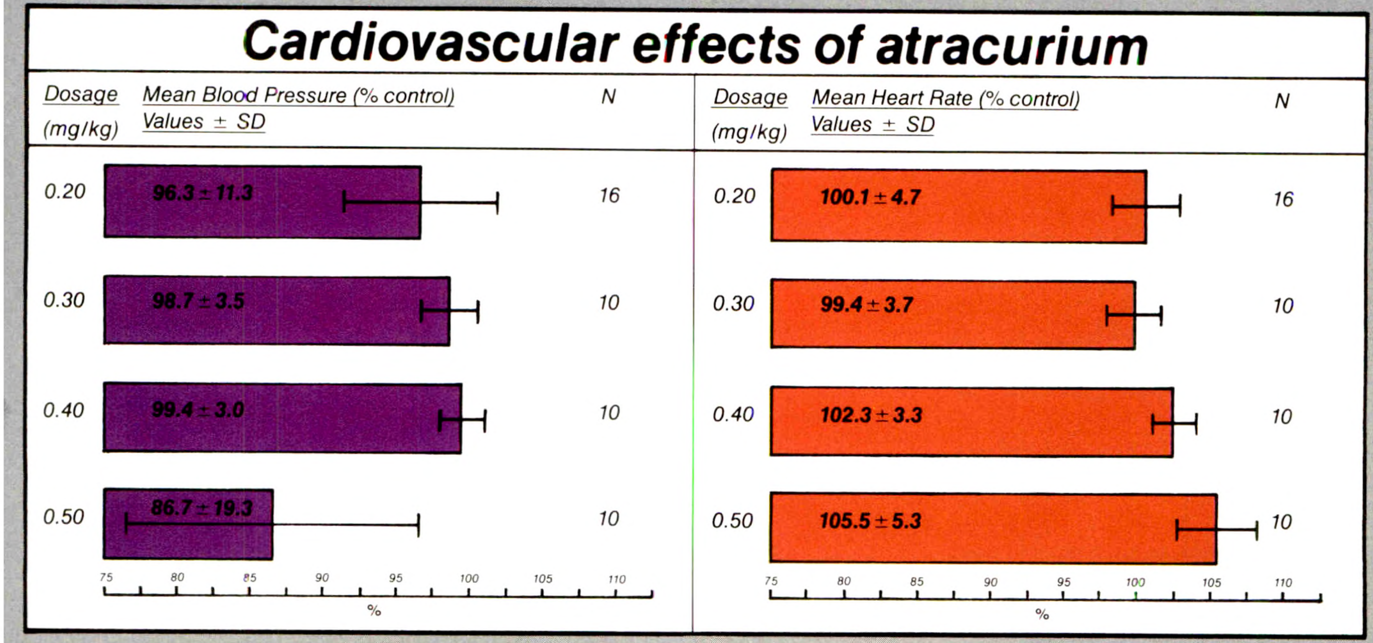
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.



Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative...."[1]

Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium[4]

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.

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TRACRIUM® INJECTION
(atracurium besylate)

TRACRIUM® INJECTION
(atracurium besylate)

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest tachycardia, cyanosis, and apnea, which have been reported t occur in approximately one in 100,000 patients.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg with halothane, which has only a marginal (approximately 20% potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade o difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul) Box of 10 ampuls (NDC-0081-0940-10).

Store under refrigeration at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

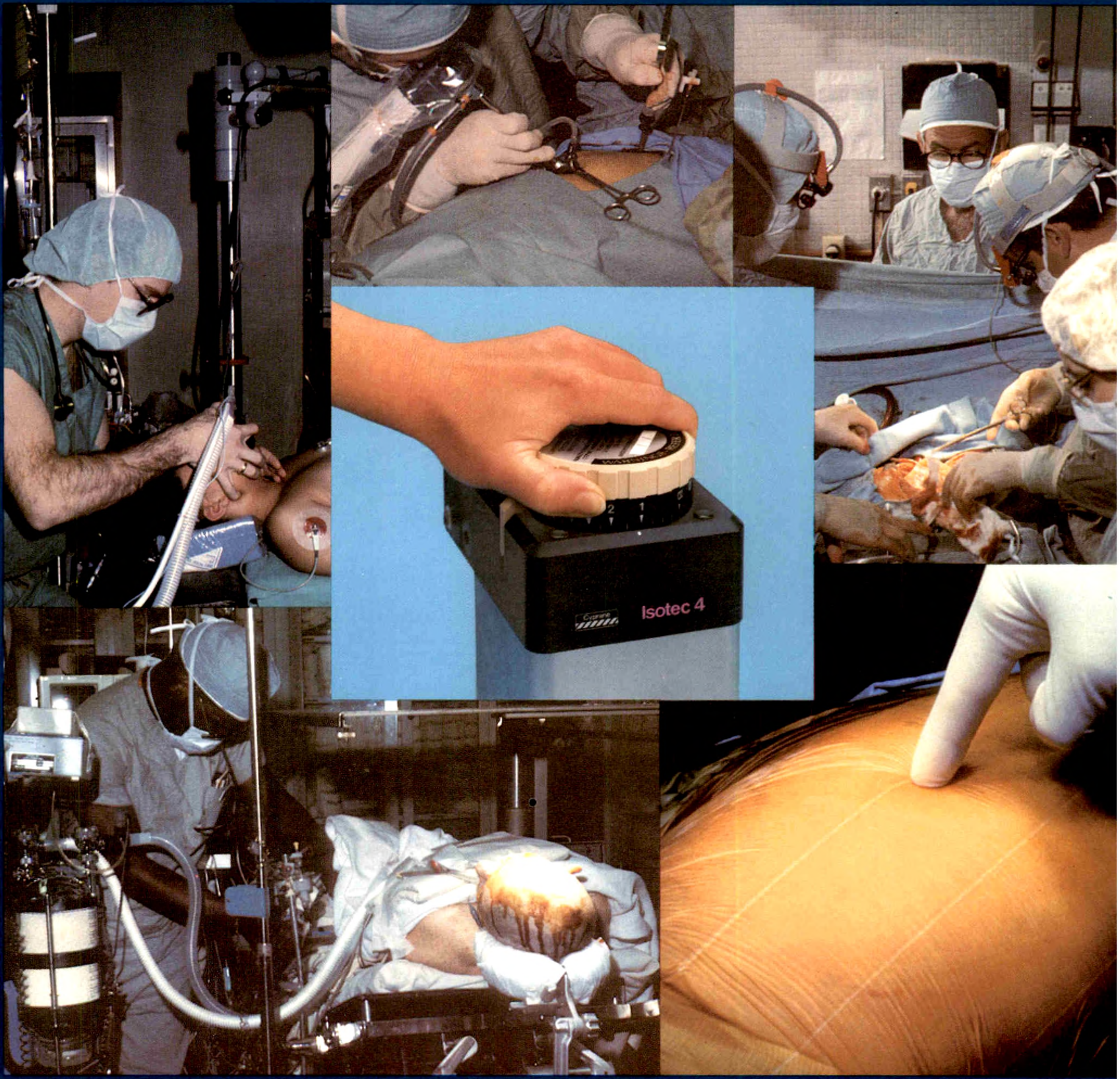
U.S. Patent No. 4179507

Printed in U.S.A. 84-TRA-4

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

TRACRIUM INJECTION
(atracurium besylate)

Forane® (isoflurane)
The Versatile Anesthetic

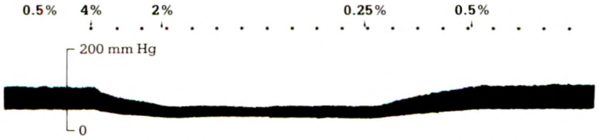


Anaquest

Forane® (isoflurane) The Versatile Anesthetic

A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

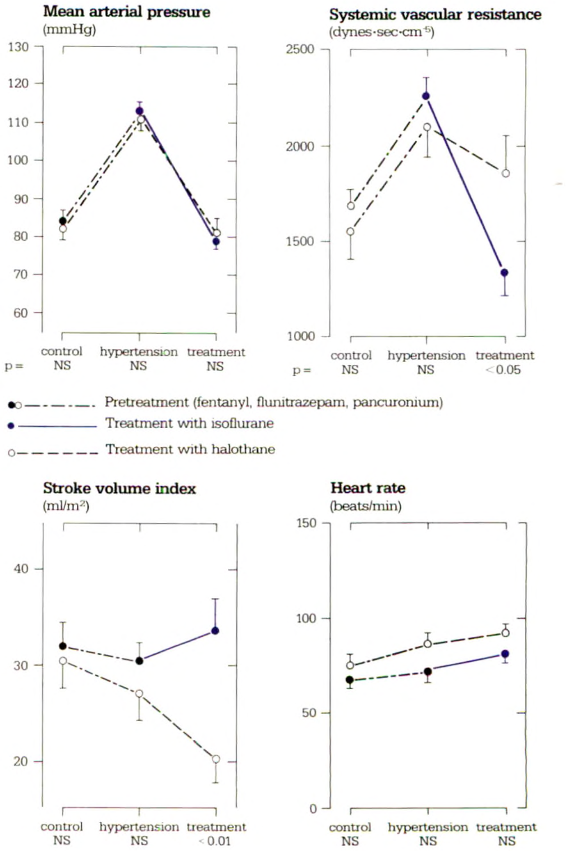
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surger (Adapted from Hess et al[3]).



Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)

Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8] *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983. 2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981. 7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

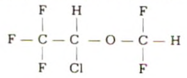
For complete use information, please see following page.

Forane® ...a product of original Anaquest research
(isoflurane)

Forane® ...The Versatile Anesthetic
(isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$F-\underset{F}{\overset{F}{C}}-\underset{Cl}{\overset{H}{C}}-O-\underset{F}{\overset{F}{C}}-H$$

Some physical constants are:

Molecular weight		184.5
Boiling point 760 mm Hg		48.5 °C (Uncorr.)
Refractive index n_D^{20}		1.2990—1.3005
Specific gravity 25°/25 °C		1.496
Vapor pressure in mm Hg.**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = {}^\circ C + 273.16\ (\text{Kelvin})$$

Partition coefficients @ 37 °C	
Water/gas	0.61
Blood/gas/gas	1.43
Oil/gas	90.8
Partition coefficients @ 25 °C—rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9 %
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitorus oxide at 900 joules/sec and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anaesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

Age	100 % Oxygen	70 % N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administerd epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known senitivity to FORANE (isoflurane) or other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing enivronment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and M.A.C. (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See Clinical Pharmacology.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at ½, ⅛, and 1/32 M.A.C. for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting, and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\%\ \text{isoflurane} = \frac{100\ P_V F_V}{F_T(P_A - P_V)}$$

where P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (ml)
F_T = Total gas flow (ml)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbituate. Inspired concentrations of 1.5 to 3% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia my be sustained with a 1.0-2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5% to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

Anaquest Forane® (isoflurane)

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Telex 910 286 2792
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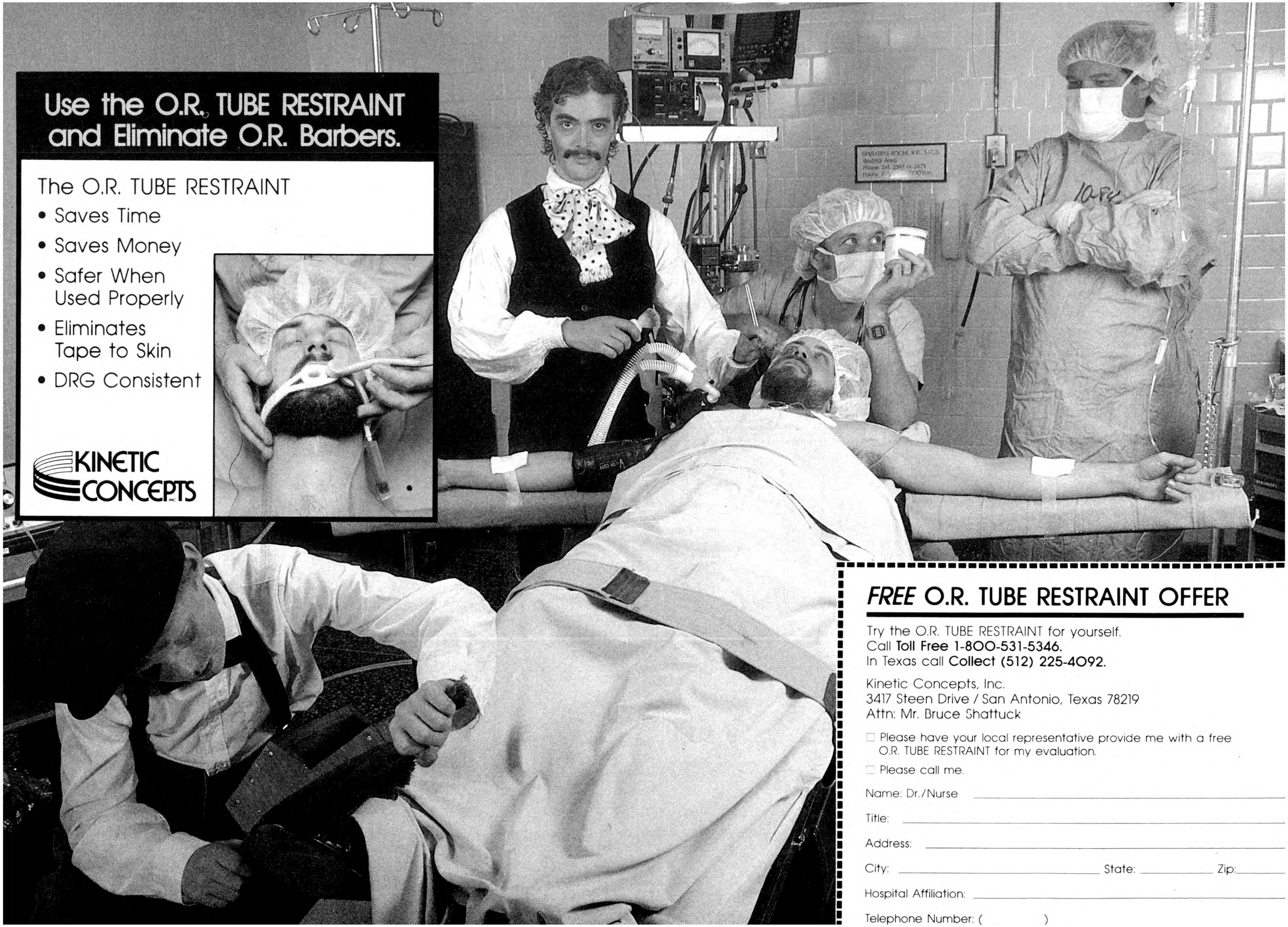

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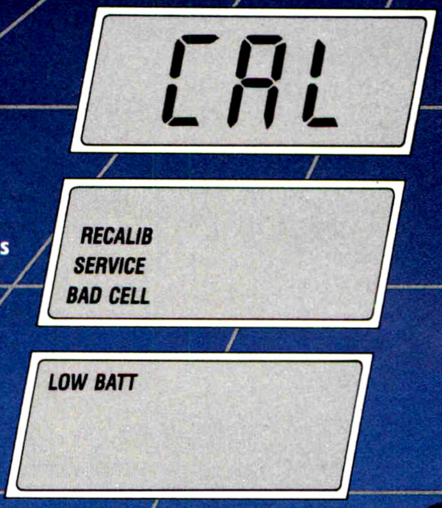

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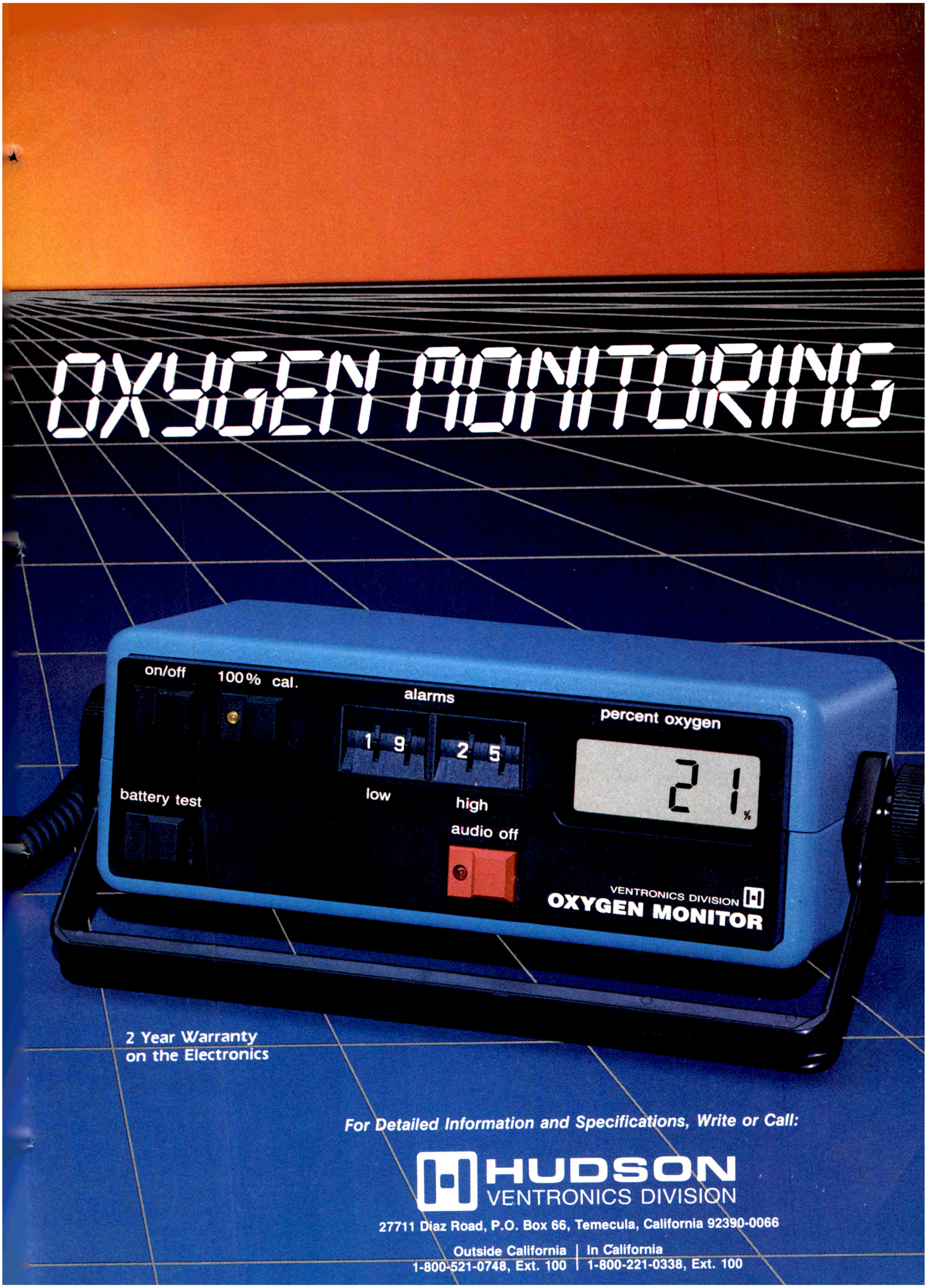

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PLEASE CONSULT FULL PRESCRIBING INFORMATION. A SUMMARY FOLLOWS:

CONTRAINDICATIONS: Obstetric paracervical block anesthesia; use in this technique has resulted in fetal bradycardia and death. Known hypersensitivity to the drug or to any amide-type local anesthetic, or to other components of MARCAINE solutions.

WARNINGS

THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Local-anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection—intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types; severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended.

Mixing, or a prior or intercurrent use, of any other local anesthetic with MARCAINE cannot be recommended because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

PRECAUTIONS: General: Safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have I.V. fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

Epidural Anesthesia: The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. During an epidural procedure, it is recommended that a test dose be administered initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. Clinical conditions permitting, the test dose should contain epinephrine (10-15 μg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect unintended intrathecal injection. This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or, in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 μg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart block.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response; ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use these agents concurrently, their combined action on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduction are potentially triggering agents for familial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene I.V. (see prescribing information before use), and other supportive measures.

Use in Head and Neck Area: Small doses of local anesthetics injected into the area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported and may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored constantly, with resuscitative equipment and personnel immediately available if needed. Do not exceed dosage recommendations. (See DOSAGE AND ADMINISTRATION.)

Use in Ophthalmic Surgery: With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

Use in Dentistry: Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa; advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

Information for Patients: When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or other possible adverse occurrence noted in package insert.

Clinically Significant Drug Interactions: Administering local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided; in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

(continued on next page)

Marcaine® HCl
(bupivacaine HCl injection, USP) with or without epinephrine 1:200,000

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.
Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)
Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.
Nursing Mothers: It is not known whether local anesthetics are excreted in human milk; because many drugs are, administer with caution.
Pediatric Use: Without further experience in children under 12, MARCAINE is not recommended for this group.
ADVERSE REACTIONS: A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.
Systemic: The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.
Central Nervous System: Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.
Cardiovascular: High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)
Allergic: Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.
Neurologic: Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug used, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinals are characterized by leg paralysis, loss of consciousness, respiratory paralysis, and bradycardia. Effects following epidural or caudal anesthesia may include: spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.
OVERDOSAGE: Acute emergency during therapeutic local anesthesia is generally related to high plasma levels or unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. *The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus I.V. injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg I.V. bolus of diazepam, or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS, respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of I.V. fluids and, when appropriate, a vasopressor dictated by the clinical situation (eg, ephedrine or epinephrine to enhance myocardial contractile force).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis; with bupivacaine, within a minute of onset. These observations suggest that O_2 consumption and CO_2 production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen; if not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur; underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous in pregnant women. The parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished. (See Labor and Delivery in PRECAUTIONS.)
Composition of Marcaine Solutions: 0.25%—each mL contains 2.5 mg bupivacaine; 0.5%—each mL contains 5 mg bupivacaine; 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple-dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothioglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium.

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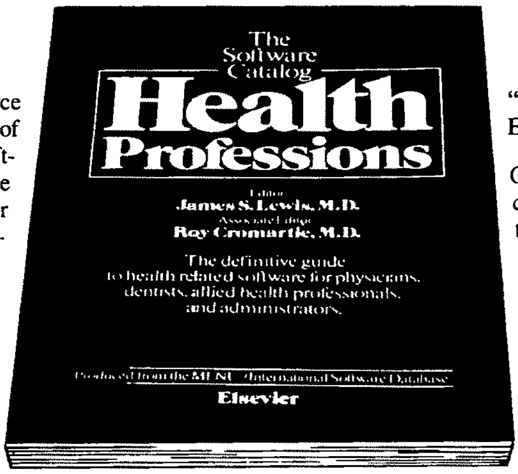

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Health Professions

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Editorials

Is There Light at the End of the Tunnel?

In their article "Choline Uptake, Acetylcholine Synthesis and Release, and Halothane Effects in Synaptosomes," Johnson and Hartzel have piled one more stone on the wall of confusion that obscures the mechanism of inhalation anesthesia. The authors studied four parameters of synaptic function: choline uptake, choline acetyltransferase, acetylcholine synthesis, and acetylcholine release (1). When they found that 3% halothane at 32°C reduced three of the four parameters, they moved the discussion immediately to considering molecular theories of anesthesia. When they found that one of three parameters that was decreased exhibited "competitive-like" inhibition of choline uptake, they concluded that their data support theories of anesthesia that postulate direct binding of anesthetics to proteins.

Several thousand papers have been published that describe the increase or decrease of some physiological parameter as a function of some concentration of inhalation anesthetic. After all this effort, why don't we know the mechanism of anesthetic action or even the site of anesthesia in the nervous system? An analysis of the paper by Johnson and Hartzell may answer that question.

The authors studied 3% halothane at 32°C. If one converts that concentration to the equivalent at 37°C, it would be at least 3.6% (2). The MAC for halothane at 37° in a rat is approximately 1% and is a very steep sigmoidal curve such that if 50% of the animals move in response to surgical stimulation at 1%, then more than 90% of the animals move at 0.9% and only a few percent move at 1.1% (3). Why did Johnson and Hartzell conduct their study with 3% halothane when that concentration is three times MAC and about twice the LD_{50} for halothane? My guess is that the dose–response curves for the parameters of choline uptake, acetylcholine synthesis, and acetylcholine release are also steep sigmoidal curves with ED_{50} values near 3% and almost nothing happens at 1% halothane. If I am wrong, I can only wish that the authors had included 1% halothane in their study so that I would have some confidence in using their data to guide my thinking about what goes on during in vivo anesthesia. If I am right, then choline uptake, acetylcholine synthesis, and acetylcholine release have nothing to do with the process of inhalation anesthesia.

I am also concerned that the authors went rather quickly from presentation of their own results to a discussion of what theories of anesthesia they seem to support. They neglected to compare their results with results of other similar experiments performed in other laboratories. Not surprisingly, the idea that inhalation anesthetics affect the synaptic transmission process has received a lot of attention in the last few decades. Many of the published results in the anesthesia literature differ with each other and with the results presented by Johnson and Hartzell. They differ, not only in the broad sense of whether anesthetics alter acetylcholine uptake, acetylcholine release, acetycholine action at the postsynaptic ending, or act on a host of other sites and transmitters, but quantitatively with the results of the particular measurements reported by the present authors.

In summary, I don't want to squeeze the paper by Johnson and Hartzell into an overfull file drawer with a note on it that the anesthetic concentration is high and the results don't seem to agree with other laboratories. I would like to know what effect a 1 MAC concentration has at 37° on the systems studied, and what improvements in methodology the authors have made that makes their results correct and why the results of preceding studies are flawed. Then we can have a useful discussion about molecular theories of anesthesia.

James R. Trudell, PhD
Department of Anesthesia
Stanford University School of Medicine
Stanford, CA 94305

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In Vivo MAC Values and In Vitro Experimentation

In our article, "Choline Uptake, Acetylcholine Synthesis and Release, and Halothane Effects in Synaptosomes," we have shown in cholinergic nerve terminal preparations obtained from rat cerebra that halothane affects neurotransmitter precursor uptake, neurotransmitter synthesis, and neurotransmitter release (1). Synaptosomes are membrane-enclosed nerve endings formed by gentle disruption of brain tissue. They contain within their membrane boundary all the necessary components for neurotransmitter synthesis, storage, and release. Rat brain cerebral synaptosomes present an in vitro model of the nerve terminal that is totally free of all conduction effects and all other in vivo physiological influences such as neuropeptides and hormones. Therefore, a direct and thorough examination of nerve terminal responses that are required for presynaptic neural transmitter processing can be accomplished in this system free of nerve conduction effects, free of inhibitory and excitatory impulses from other neurons, and free of all other in vivo physiological influences.

The results reported by Johnson and Hartzell (1) have been criticized by Trudell (2) largely on the basis that the halothane concentration used in these experiments exceeded in vivo MAC values. (The concept of MAC and the advantages and limitations of MAC usage in anesthesia have been amply described by Eger (3) and will not be further elaborated upon.) We take this opportunity to examine the concept that physiological and biochemical parameters measured in vitro must respond within the pharmacologically significant dose range obtained for in vivo MAC in order to be considered contributory to in vivo anesthesia mechanisms. There are many topics that should be included in this discussion; however, for the sake of brevity, we will present only three key concepts: solubility of halothane; in vivo physiological modulation of cellular response; and biochemical catalysis and control.

Solubility of Halothane

It is well established that halothane is one-third as soluble in buffered saline solution as in blood. Thus the concentration of halothane in saline at 3% gas-phase halothane would approximate the same concentration of halothane in blood at 1% gas-phase halothane (4). A second consideration with regard to halothane concentration in synaptosomes is the solubility of halothane in the synaptoplasm. No information is available concerning final halothane concentrations in the in vivo nerve terminal with a full complement of organelles, proteins, and lipids. However, it is doubtful whether the ruptured and resealed synaptosome can solubilize halothane to the same extent as in vivo terminals. And finally, if the halothane concentrations in both the bathing medium and synaptoplasm are altered (decreased), it is reasonable to assume that the medium–membrane and membrane–synaptoplasm interfacial concentrations of halothane are significantly changed as well (5). These altered solubility effects are directly applicable to considerations of reversible halothane inhibition of choline transport: the receptor initially involves the medium–membrane interface and acetylcholine release potentially involves both membrane interfaces in the in vitro synaptosomes.

Modulation of Cellular Responses

Anesthetic effects on the modulation of neuronal conduction and synaptic transmission and the sensorimotor modulation system are described by Kendig (6) and Angel (7), respectively. The almost overwhelming complexity of the neuronal system and interacting networks prompted us to seek a simpler model system to investigate the possible role of halothane in presynaptic transmission events of transport, synthesis, and release. That the synaptosomes do not reveal the in vivo sensitivity to halothane observed for induction of anesthesia should be neither surprising nor unexpected due to the many modulatory effectors (both positive and negative) available to the in vivo cerebral nerve terminals.

Catalysis and Control

Porteous has pointed out that "a number of important biological functions, which must have a molecular basis, have not yielded to the traditional 'fractionate and analyse' approach of the biochemist" (8). One

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example he presents is "the capacity of central neuronal networks to capture, sort, store and recall input signals and to modify these capacities with the passage of time" (8). These considerations, along with control theory concepts relating to embryogenesis, differentiation, genetic dominance, and steady-state metabolic control, have prompted a small, but steadily growing, number of biochemists to reexamine intracellular and extracellular variables and parameters that contribute to the magnitude of flux through various pathways (see Westerhoff et al. for review (9)). A total understanding of a physiological response to a pharmacological effector requires molecular information concerning events that occur within a functionally intact cell involving interactions among all system components including the immediate environment, and all events must be analyzed with respect to time. Some of these answers can be gained only with an understanding of the kinetics and energetics of fluxes through these complex interacting systems. However, these complex systems require as many windows of understanding as possible to complete a reasonable picture. It is for this one view that we launched our investigation of halothane effects on presynaptic transmission events.

Charles R. Hartzell, PhD
Gail V.W. Johnson, PhD
Alfred I. duPont Institute
PO Box 269
Wilmington, DE 19899

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Cardiac Electrophysiologic and Hemodynamic Effects Related to Plasma Levels of Bupivacaine in the Dog

Ragnar Hotvedt, MD, Helge Refsum, MD, PhD, and Knut G. Helgesen, MD

HOTVEDT R, REFSUM H, HELGESEN KG. Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dog. Anesth Analg 1985;64:388–94.

To investigate electrophysiologic and hemodynamic responses to various plasma levels of bupivacaine, especially those in the range normally seen during regional anesthesia, bupivacaine was given intravenously as a bolus dose followed by continuous infusion in pentobarbital-anesthetized dogs. Cardiac electrophysiology was studied by His bundle electrography, programmed electrical stimulation, and monophasic action potential recordings. At plasma bupivacaine concentrations below 1000 ng/ml, no significant electrophysiologic or hemodynamic effects were observed. This indicates that systemic responses to absorbed bupivacaine do not contribute to the cardiac electrophysiologic effects recently demonstrated during thoracic epidural analgesia. At a plasma level of about 2000 ng/ml, a level occasionally achieved during regional anesthesia, bupivacaine prolonged impulse conduction time in all parts of the heart, prolonged atrial and AV nodal refractoriness, decreased left ventricular inotropy, but had no effect on ventricular refractoriness or monophasic action potential duration. These electrophysiologic effects may enhance susceptibility to reentrant arrhythmias.

Key Words: ANESTHETICS, LOCAL—bupivacaine. HEART, MYOCARDIAL FUNCTION—bupivacaine.

Increasing attention has been directed recently to possible cardiac effects of bupivacaine. This is due in part to publication of several reports of severe cardiovascular complications associated with regional blocks induced with this local anesthetic (1–4). The complications have been presumed to be caused by intravascular injection in most of the cases. However, intravascular injection usually has not been documented. The question, therefore, arises as to whether bupivacaine after normal absorption during regional anesthesia has systemic effects that may influence cardiac function.

Certain forms of regional anesthesia may also have cardiac effects caused by simultaneous blockade of the cardiac sympathetic innervation. It has been shown recently that thoracic epidural analgesia induced with bupivacaine has significant cardiac electrophysiologic and hemodynamic effects (5–7). However, contributional effects from bupivacaine absorbed systemically have not been ruled out. Therefore, the aim of this study was to investigate cardiac electrophysiologic and hemodynamic effects of bupivacaine at various plasma levels, especially plasma levels in the range normally seen during clinical regional anesthesia.

Methods

Animal Preparation

We used eight mongrel dogs of either sex, weighing 15–25 kg (mean 17.4). Anesthesia was induced with sodium pentobarbital 25 mg/kg intravenously, and maintained with a continuous intravenous infusion of 3.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ (8). The dogs were ventilated through endotracheal tubes with room air using a volume-controlled respirator. Arterial blood gas tensions and acid–base balance were measured repeatedly throughout the experiments, and the body temperature was maintained at 37 ± 3°C using an infrared lamp.

Heart catheterization was performed via femoral vessels under fluoroscopic control. A 5F PC-350 Millar Micro-tip pressure transducer catheter was introduced into the left ventricle. At spontaneous heart rate, left ventricular blood pressure was measured, and the first derivative of the pressure (*dP/dt*) signal was computed with a linear frequency response of 160 Hz. The signals were recorded on a Mingograf 82 (Elema Schönander, Stockholm, Sweden). A trian-

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Address correspondence to Dr. Hotvedt, Institute of Medical Biology, University of Tromsö, Box 977, N-9001 Tromsö, Norway.

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gular signal with a known slope was substituted for pressure signals to calibrate *dP/dt*. Aortic blood pressure was measured at spontaneous heart rate with a catheter in the descending aorta, using a Statham transducer P 23 De. The signals were recorded on a Beckman R411 Dynograph Recorder. A continuous intravenous infusion of 0.9% NaCl 2–3 $ml\cdot kg^{-1}\cdot hr^{-1}$ was given throughout the experiments. The urinary bladder was catheterized.

Cardiac Electrophysiology

A 6F quadripolar electrode (USCI) was placed in the sinus node region, and atrial pacing was performed with the distal (1) cathodal and the proximal (4) anodal electrode. High right atrial (HRA) recordings were done with electrodes 2 and 3. A 6F tripolar electrode (USCI) was placed across the atrioventricular junction. The position was ascertained by a bi- or triphasic deflection of the bundle of His between the P wave and the QRS complex of the external electrocardiogram. Ventricular pacing was performed with a 4F bipolar electrode (USCI). Recordings were done on the Mingograf 82 with three external leads (I, II, and III), and two bipolar intracardiac registrations (His and HRA). All recordings were done at paper speed of 250 mm/sec.

Monophasic action potential (MAP) recordings were obtained from the outflow tract of the right ventricle in six dogs (9). An 8F radio-opaque close bipolar suction electrode catheter was introduced from a femoral vein and pushed to the right ventricle under fluoroscopic control. The catheter was slightly pressed against the endocardial wall, and a three-way stopcock allowed either infusion of saline through the catheter or application of suction −350 mm Hg. The close bipolar signal between the electrode terminals, both situated at the end of the catheter 1 mm apart, was preamplified with a high input impedance (30 MΩ) differential DC recording system. The signals were recorded on the Mingograf 82 at paper speed of 250 mm/sec. The amplitude of the MAP was measured in mV as the distance from the diastolic baseline to the highest point of the plateau. The duration of MAP was measured at levels of 50 and 90% repolarization ($VMAPD_{50}$ and $VMAPD_{90}$, respectively), as defined by the percent of the plateau amplitude. The values were obtained from the median of 5 MAPs, where recordings with a lower amplitude than 25 mV were discarded. After each recording, the suction electrode catheter was withdrawn slightly, and advanced again to contact the endocardium when further recordings were required.

Pacing as well as programmed stimulation were carried out using a stimulator that delivered square-wave impulses of 1.8 msec duration (Medtronic 5325 Programmable Stimulator). The output was set at twice the diastolic threshold. Intracardiac conduction times were measured at spontaneous heart rate and at pacing at frequencies of 170, 200, 230, and 260 beats/min. Refractoriness was measured with a premature impulse (st 2) delivered after each train of eight regular stimuli (st 1), the interval (st 1–st 2) was reduced in steps of 10–5 msec until no further response could be obtained.

The following measurements were made: PA interval, stA interval, AH interval, HV interval, QRS width, functional refractory period (FRP) of the AV node and the right ventricle, and effective refractory period (ERP) of the right atrium and ventricle, according to conventional definitions (5,10).

Plasma Bupivacaine Determination

Bupivacaine concentrations in plasma were determined at Astra Läkemedel AB, Research and Development Laboratories, Södertälje, Sweden, by selected ion monitoring. Plasma was separated from arterial blood samples by centrifugation for 10 min at 4°C, and kept frozen at −20°C until analysis.

To 1.00 ml of plasma in a 10-ml tube were added 1.00 ml (1 μg) of an aqueous solution of the internal standard (1-n-pentyl-2-(2′,6′-xylylcarbamoyl)-piperidine hydrochloride), 0.50 ml of 10% sodium bicarbonate solution, and 3 ml of methylene chloride, and the tube was rotated for 15 min in a rotary mixer. After centrifugation, the organic phase was transferred to a 3 ml silanized glass tube and evaporated to dryness under nitrogen at 40°C. The residue was dissolved in 100 μl of ethanol. An LKB model 2091-051 gas chromatograph-mass spectrometer with an LKB 2091-710 multiple ion detector was used for the quantitative analysis. The ions m/z 140 (base peak for bupivacaine) and 154 (base peak for the internal standard) were monitored. The separation was carried out on a glass column, 0.9 m × 2 mm inner diameter, packed with 3% OV-17 on Supelcoport (80–100 mesh) at column temperature 240°C. The approximate retention times were 100 sec (bupivacaine) and 150 sec (internal standard).

Protocol

Hemodynamic and electrophysiologic control recordings were taken 20 min after finishing the operative procedures. Each dog then received bupivacaine, given as three consecutive intravenous bolus doses, each immediately followed by continuous in-

Table 1. Hemodynamic Effects after Intravenous Administration of Bupivacaine[a]

	Control values	Changes at different plasma levels of bupivacaine (ng/ml)		
		231 ± 21	880 ± 79	2435 ± 279
HR (beats/min)	150 ± 10	0 ± 3	1 ± 4	−1 ± 5
$\bar{P}$ao (mm Hg)	131 ± 5	0 ± 2	−2 ± 2	−2 ± 2
LV *dP/dt* max (mm Hg/sec)	2980 ± 384	−207 ± 155	−373 ± 194	−624 ± 205[b]

[a] Values are mean ± SEM, $n = 8$.
[b] $P < 0.05$.
Abbreviations: HR, spontaneous heart rate; $\bar{P}$ao, mean aortic blood pressure; LV *dP/dt* max, left ventricular *dP/dt* max.

travenous infusion. The durations of the infusion periods were 40 ± 3, 37 ± 3, and 37 ± 2 min (mean ± SEM, $n = 8$), respectively. Recordings were done during the infusion, and started 15 min after the bolus dose. The doses of bupivacaine were the following: first bolus 0.1 mg/kg and infusion 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, second bolus 0.2 mg/kg and infusion 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and third bolus 0.4 mg/kg and infusion 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Each new bolus was given immediately after the end of the foregoing recording period. Arterial blood samples for bupivacaine analysis were taken at the beginning and at the end of each recording period.

Statistics

Each dog served as its own control. For statistical evaluation, two-way analysis of variance was employed (11). When this analysis indicated significant differences, the groups were compared using the Q method based on a studentized range (12). Statistical significance was assumed with $P < 0.05$. Values are given as mean ± SEM.

Results

Plasma Levels of Bupivacaine

During the first recording period, the plasma concentration of bupivacaine decreased from 250 ± 24 to 213 ± 21 ng/ml (mean ± SEM, $n = 8$) ($P < 0.05$). During the second recording period, the concentration increased from 828 ± 68 to 932 ± 93 ng/ml ($P < 0.05$), and during the third recording period, from 2256 ± 124 to 2614 ± 464 ng/ml (not significant). The durations of the three recording periods were 25 ± 3, 22 ± 3, and 22 ± 2 min (mean ± SEM). The mean bupivacaine levels during each recording period, calculated as the mean of the initial and final concentrations obtained in each dog, were 231 ± 21, 880 ± 79, and 2435 ± 279 ng/ml, respectively.

In two dogs, atrial pacing was not possible at the highest bupivacaine level, in spite of increasing the stimulator output tenfold. In the remaining six dogs, bupivacaine concentrations during the three recording periods were 220 ± 26, 843 ± 83, and 2030 ± 104 ng/ml (mean ± SEM). Of the eight dogs, the two in which atrial pacing was not possible during the last recording period had the highest plasma concentrations: mean values of 3083 and 4221 ng/ml, respectively.

During ventricular pacing, the dog with the highest bupivacaine concentration (5742 ng/ml) suddenly developed ventricular fibrillation. We did not succeed in resuscitating this dog with external heart compression, DC shocks, or different pacing techniques. Ventricular pacing was performed without complications in the remaining dogs. In the six dogs in which monophasic action potential recordings were obtained, the bupivacaine concentration during the three recording periods were 221 ± 26, 927 ± 99, and 2138 ± 187 ng/ml, respectively.

Hemodynamic Effects

No significant changes were found in spontaneous heart rate or mean aortic blood pressure at the three different plasma levels of bupivacaine (Table 1). A reduction in left ventricular *dP/dt* max was seen with increasing plasma bupivacaine levels, but this reduction was statistically significant only at the highest plasma concentration.

Intracardiac Impulse Conduction

Mean control values (±SEM) for intraatrial conduction time were 28 ± 2 msec (PA interval at spontaneous heart rate, $n = 8$) and 33 ± 3 msec (stA interval at pacing rate 230 beats/min, $n = 6$); for AV nodal conduction time, 66 ± 6 msec (AH interval at spontaneous rate, $n = 8$) and 85 ± 11 msec (at 230 beats/min, $n = 6$). His-Purkinje conduction time (HV interval) was 23 ± 2 msec, and the QRS width 59 ± 2 msec (both at spontaneous heart rate, $n = 8$, and at 230 beats/min, $n = 6$).

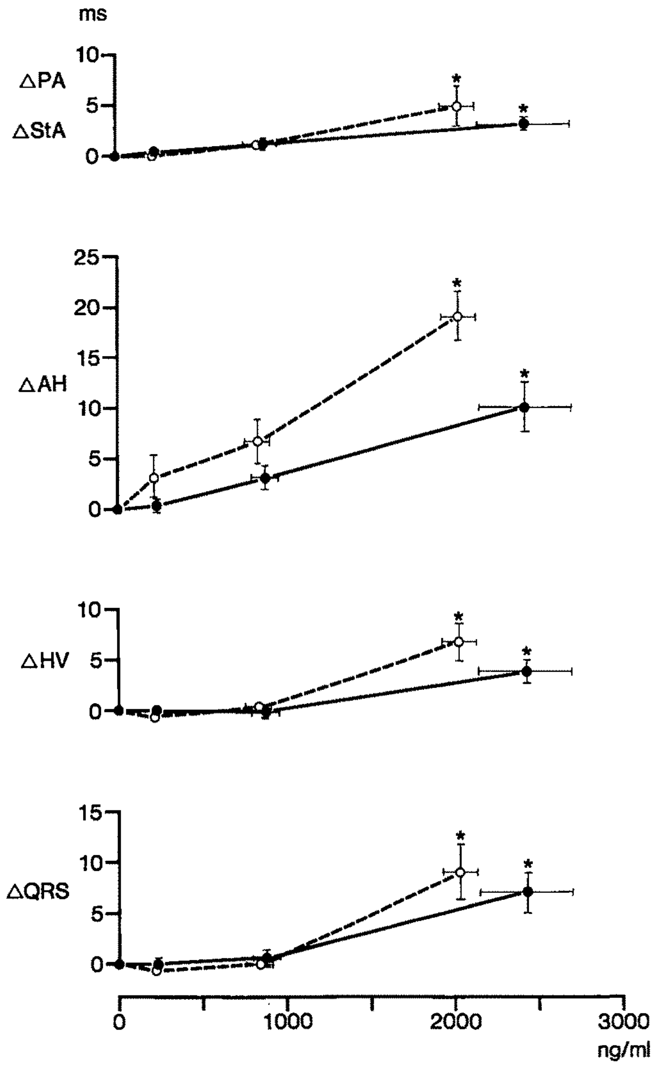

Figure 1. Changes in intraatrial (PA and stA intervals), AV nodal (AH interval) and His-Purkinje (HV interval) impulse conduction times, and QRS width at different plasma concentrations of bupivacaine. Values are mean ± SEM. Symbols: O– – – –O, pacing at 230 beats/min. $n = 6$; ●——● = spontaneous heart rate, $n = 8$. $*P < 0.05$.

After bupivacaine administration, no significant changes were seen in the intracardiac impulse conduction at the two lowest plasma concentrations (Fig. 1). However, at the highest plasma concentration, the intraatrial, AV nodal and His-Purkinje impulse conduction times, and the QRS width increased significantly, both at spontaneous heart rate and at the different pacing frequencies. At the highest plasma levels, the prolongation of the impulse conduction times increased with increasing pacing frequencies: at pacing rates of 170, 200, and 260 beats/min, the increases in stA interval were 3.2 ± 1.0, 4.4 ± 1.7, and 6.3 ± 1.3 msec (mean ± SEM), respectively. The increases in HV interval were 4.8 ± 1.1, 6.0 ± 1.5, and 8.0 ± 1.9 msec, respectively; in QRS width, 6.8 ± 2.1, 7.6 ± 2.2, and 10.3 ± 2.9 msec, respectively. The AH interval increased 6.8 ± 2.2 and 10.0 ± 3.1 msec at 170 and 200 beats/min, respectively. At 260 beats/min, AV block of second degree (Wenckebach block) was induced in two out of six dogs, while the AH interval was 21.0 ± 2.1 in the remaining four dogs.

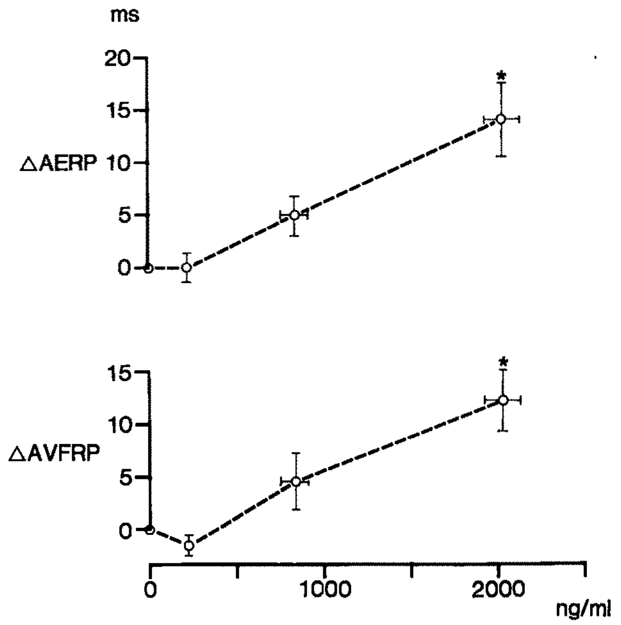

Figure 2. Changes in atrial and AV nodal refractoriness at different plasma concentrations of bupivacaine. Abbreviations: AERP, atrial effective refractory period; AVFRP, AV nodal functional refractory period. Values are mean ± SEM, $n = 6$. $*P < 0.05$.

Refractoriness and Action Potential Duration

At a pacing frequency of 230 beats/min, the control value for atrial effective refractory period was 98 ± 5 msec (mean ± SEM, $n = 6$), and for AV nodal functional refractory period, 228 ± 13 msec (mean ± SEM, $n = 6$). The atrial and AV nodal refractoriness did not change at the lowest plasma levels of bupivacaine, but at the highest level a significant increase was seen (Fig. 2). Also at pacing rates 170, 200, and 260 beats/min, bupivacaine at the highest plasma level significantly increased atrial and AV nodal refractoriness.

As shown in Table 2, bupivacaine did not significantly change the ventricular effective (VERP) or functional (VFRP) refractory period at any of the three plasma levels. Neither 50 nor 90% repolarization times for the monophasic action potentials (VMAPD_{50} and VMAPD_{90}) significantly changed at any of the three bupivacaine plasma levels. This lack of effect on ventricular MAP duration and refractoriness was found at spontaneous heart rate and at all pacing rates from 170 to 260 beats/min.

Table 2. Ventricular Refractoriness and Action Potential Duration after Intravenous Administration of Bupivacaine[a]

	Control values (msec)	Changes (msec) at different plasma levels of bupivacaine (ng/ml)		
		221 ± 26	927 ± 99	2138 ± 187
VERP[c]	119 ± 8	0 ± 2	4 ± 3	5 ± 1
VFRP[c]	159 ± 5	−1 ± 2	3 ± 1	0 ± 1
VMAPD_{50}^{b}	128 ± 10	−1 ± 2	−2 ± 2	0 ± 3
VMAPD_{50}^{c}	119 ± 9	1 ± 2	0 ± 3	2 ± 3
VMAPD_{90}^{b}	163 ± 13	−3 ± 3	0 ± 3	1 ± 4
VMAPD_{90}^{c}	152 ± 11	−2 ± 2	−2 ± 3	0 ± 2

[a] Values are mean ± SEM, $n = 6$. None of the changes were statistically significant.

[b] Spontaneous heart rate.

[c] Pacing rate 230 beats/min.

Abbreviations: VERP, ventricular effective refractory period; VFRP, ventricular functional refractory period; VMAPD_{50} and VMAPD_{90}, Time for 50 and 90% repolarization of ventricular monophasic action potentials, respectively.

Discussion

In this experimental study we investigated the cardiac electrophysiologic and hemodynamic effects at different plasma levels of bupivacaine. At bupivacaine concentrations below 1000 ng/ml, no significant effects were seen, but at about 2000 ng/ml, impulse conduction time in all parts of the heart was prolonged, atrial and AV nodal refractoriness was prolonged, and left ventricular inotropy decreased.

We recently showed that thoracic epidural analgesia induced with bupivacaine (0.7 mg/kg) significantly prolongs AV nodal impulse conduction time and refractoriness in the dog, as well as prolonging ventricular refractoriness and monophasic action potential duration (5). Thoracic epidural analgesia also had marked hemodynamic effects (6). We measured plasma levels of bupivacaine after thoracic epidural injection of 0.7–1.2 mg/kg in dogs (5,7). The plasma levels varied considerably. In six of the seven dogs, peak plasma levels of bupivacaine averaged 425 ng/ml (range 153–905 ng/ml). At the time of maximal electrophysiologic effects, however, the plasma level had decreased to 239 ng/ml (range 114–431 ng/ml). Comparing these results with the results of the present study indicates that systemic effects from absorbed bupivacaine do not contribute to the observed cardiac electrophysiologic and hemodynamic effects of thoracic epidural analgesia. These effects of thoracic epidural analgesia are probably mainly caused by a reduced sympathetic neural influence on the heart. In one dog, however, a peak plasma concentration of 2696 ng/ml was achieved. Although at the time of maximal electrophysiological effects the plasma level was reduced to 646 ng/ml, an initial contributing effect from absorbed bupivacaine probably cannot be excluded in this dog.

It is well known that plasma levels of local anesthetics vary widely in patients treated with different regional anesthetic techniques. Systemic absorption if related primarily to site of injection, dosage, and presence or absence of vasoconstrictor agent in the anesthetic solution. Mean peak plasma concentrations of 3290 and 2330 ng/ml have been measured after bilateral intercostal and lumbar epidural nerve blockade induced with 400 and 225 mg of bupivacaine, respectively (13,14). Bupivacaine plasma levels up to 3330 ng/ml have been found after axillary plexus blockade (15) and have recently been estimated to have been higher than 1800 ng/ml during Bier block with the cuff still inflated (3,16). This implies that plasma concentrations of bupivacaine that have significant cardiac electrophysiologic and hemodynamic effects may be achieved in patients during different regional nerve blockades in the absence of intravascular injection.

The present study was carried out in dogs during pentobarbital anesthesia. Several cardioactive drugs, including local anesthetics with similar effects as bupivacaine, have been demonstrated to have the same cardiac electrophysiologic effects in pentobarbital-anesthetized dogs as in humans (17,18). At plasma concentrations found with surgical anesthesia, direct effects of pentobarbital on the cardiovascular system are probably small (8,19), although an interaction of pentobarbital with the results obtained in this study cannot be excluded.

Pentobarbital has indirect cardiac effects through its influence on the autonomic nervous system. It seems to increase sympathetic (20–23), and markedly reduces vagal, nervous activity (24–26). Therefore, during pentobarbital anesthesia there will be a relative enhancement of the sympathetic nervous tone, as revealed by the high spontaneous heart rate seen in the present study. In conscious, resting humans and dogs, the heart rate is determined mainly by vagal influence (27). Apprehension and pain from surgery or other trauma, however, increase sympathetic nervous tone (28–30). Although one should be extremely careful in extrapolating from dogs to humans, the experimental model chosen to study cardiac effects of bupivacaine may thus be relevant to clinical situations in which bupivacaine is administered to patients under stress.

In the present study, bupivacaine at the highest plasma level depressed left ventricular *dP/dt* max, while heart rate and mean aortic blood pressure remained unchanged. Jorfeldt et al. (31) also found no effect on heart rate and blood pressure at similar plasma levels of bupivacaine in awake dogs. At higher doses and plasma levels, however, bupivacaine seems to have more profound hemodynamic effects. But the results of different studies have been conflicing, partly depending on whether general anesthesia was used or not. Thus bupivacaine increased heart rate and blood pressure in awake dogs and sheep (32,33), but was associated with progressive bradycardia and arterial hypotension in pentobarbital-anesthetized dogs (34). In isolated heart preparations, bupivacaine in high concentrations depresses heart rate and contractility, indicating a direct cardiodepressive effect (35–37).

We found that bupivacaine at the highest plasma level had a marked depressive effect on AV nodal impulse transmission. This is in accordance with the findings of Yoshida (38), who showed that bupivacaine, although at high concentrations, had a potent direct depressive effect on AV nodal conduction in the dog heart in situ, and those of Kotelko et al. (33), who found that bupivacaine induced AV nodal block in 60% of the conscious sheep studied. In the isolated rat heart preparation, bupivacaine markedly depressed AV nodal impulse conduction (39). However, Block and Covino (35) found the AV node to be more resistant than atrial and ventricular conduction pathways to the depressive effect of bupivacaine in the isolated rabbit heart.

Bupivacaine has been shown to protect against digitalis- and epinephrine-induced arrhythmias in anesthetized dogs (40,41). In other studies, on the contrary, bupivacaine has induced serious arrhythmias in awake sheep and lightly anesthetized cats (33,42), as well as in patients after induction of regional nerve blocks (1–4, 43). Most cardiac arrhythmias are thought to be caused by reentry phenomena, or a combination of abnormal impulse initiation and reentry. Usually a combination of slowed conduction and unidirectional conduction block provides the conditions necessary for reentry to occur. This may be seen in cardiac tissue influenced by disease, e.g., ischemia, acidosis, electrolyte disturbances, or drugs. The electrophysiologic effects of bupivacaine seen at the highest plasma levels in this study might well enhance susceptibility to reentrant arrhythmias, especially in the ventricles where impulse conduction was depressed while no change was seen in refractoriness or action potential duration. In one dog, ventricular fibrillation was induced during ventricular pacing at a very high plasma concentration of bupivacaine (which was probably caused by a maladjustment of the infusion pump).

In summary, this study indicates that systemic effects from absorbed drug do not contribute to the cardiac electrophysiologic (5) and hemodynamic (6) effects seen in dogs during thoracic epidural analgesia induced with 0.7–1.2 mg/kg bupivacaine. The effects of thoracic epidural analgesia are thus mainly caused by reduced sympathetic neural influence on the heart. At higher plasma levels that may occasionally be achieved by systemic absorption during regional anesthesia in humans, bupivacaine has, however, significant cardiac electrophysiologic and hemodynamic effects. These effects may enhance the susceptibility to reentrant arrhythmias in predisposed patients.

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Choline Uptake, Acetylcholine Synthesis and Release, and Halothane Effects in Synaptosomes

Gail V. W. Johnson, PhD, and Charles R. Hartzell, PhD

JOHNSON GVW, HARTZELL CR. Choline uptake, acetylcholine synthesis and release, and halothane effects in synaptosomes. Anesth Analg 1985;64:395–9.

Synaptosomes isolated from rat cerebra were used as a model to study the effects of halothane on choline uptake and acetylcholine synthesis and release processes. Synaptosomes are membrane-bound particles that are formed by gentle disruption of brain tissue. These particles include the presynapse, cleft, portions of postsynaptic membrane, and all other components contained in brain nerve terminals necessary for neurotransmitter synthesis, storage, and release. Halothane (3% in air, vol/vol) caused a "competitive-like" inhibition of choline uptake in synaptosomes but had no effect on the enzymatic activity of choline acetyl-transferase (ChAT). Three percent halothane depressed synaptosomal acetylcholine (ACh) synthesis by 86% while ACh release from synaptosomes was inhibited 50%. It is suggested that halothane inhibits ACh synthesis by directly interfering with the carrier-mediated transport system of choline. Since halothane also inhibits ACh release, as well as choline uptake, it is probable that the anesthetic is acting upon more than one site in these cholinergic nerve terminals. These data require an interpretive evaluation that cannot fit the "unitary" hypothesis as the mechanism of action of general anesthetics.

Key Words: ANESTHETICS, VOLATILE—halothane. ACETYLCHOLINE—cerebral. BRAIN—acetylcholine.

There is considerable evidence to implicate acetylcholine (ACh) as an important neurotransmitter for the maintenance of consciousness. It has been demonstrated that ACh is involved in cortical arousal (1) and there is excellent evidence that the ascending reticular activating system is cholinergic (2). ACh also induces firing of neurons in the sensory cortex, accompanied by long after-discharges, which are necessary for sensory awareness (3). The role of ACh in maintaining the conscious state makes it important to understand the effects of anesthetics on ACh metabolism. One of the most frequently used anesthetics for the maintenance of narcosis is halothane. Some of the effects of this anesthetic on cholinergic processes have been studied in vitro as well as in vivo. In rat brain slices (4) halothane caused a decrease in ACh content and inhibited the incorporation of label from [2-^{14}C] pyruvate into ACh by approximately 50%. Schmidt (5) demonstrated that halothane causes an increase in ACh content in the brain. The increases in ACh levels varied with the depth of anesthesia and among brain regions, with the largest increase being in the cortex. It was concluded that depression of neuronal activity during halothane anesthesia decreased the amount of ACh released, and therefore caused an elevation in the level of ACh. However, Ngai et al. (6) found that halothane treatment did not change ACh concentrations in the brain, although the turnover rate was depressed. In their conclusion, the authors stated that "the question in respect to neuronal uptake of choline and choline acetyltransferase as affected by halothane remains open for further studies. These studies are necessary because halothane decreased the turnover rate of acetylcholine uniformly in all regions of the brain (6)."

In this study we have attempted to answer the questions raised by Ngai et al. (6). We have investigated in detail the effects of halothane on cholinergic function by examining its effects on choline uptake, choline acetyltransferase activity (ChAT), and ACh synthesis and release in synaptosomes.

Methods

Synaptosomal Preparation

The synaptosome isolation procedure was modified from Booth and Clark (7). Three to six male Sprague-Dawley rats (200–250 g) from Parco Scientific Com-

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Address correspondence to Dr. Hartzell, Director of Research, Alfred I. duPont Institute, PO Box 269, Wilmington, DE 19899.

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pany (Wenonah, NJ) were sacrificed by decapitation. The brains were removed, rinsed with ice-cold isolation medium containing 0.32 M sucrose, 5 mM N-2-hydroxyethyl piperazine-N'-2-ethane sulfonic acid (HEPES), and 100 μM neostigmine; pH 7.4 and the cerebra were isolated. All preparative steps were carried out at 4°C. The cerebra were gently homogenized in 50–60 ml of isolation medium using a Dounce homogenizer (B pestle). The homogenate was sedimented at 1300 × g for 5 min at 4°C. The supernatant was removed and sedimented at 17,000 × g for 10 min. The supernatant was discarded and the pellet was suspended in 15% (wt/wt) Type 400 Ficoll to give a final Ficoll concentration of 12% (final volume approximately 25 ml). The mixture was transferred to a 40 ml polyallomer tube and covered with 10 ml of 7.5% Ficoll followed by 5 ml of isolation medium. The synaptosomal preparation in the discontinuous gradient was subjected to centrifugal force for 50 min at 96,300 × g in a Beckman L2-65B ultracentrifuge. The synaptosomal fraction at the 7.5%/12% Ficoll interface was removed and suspended in 50 ml of salt medium containing 140 mM NaCl, 5 mM KCl, 1.2 mM $MgCl_2$, 20 mM HEPES, and 100 μM ethylenediamine tetraacetic acid (EDTA), pH 7.4. The suspension was sedimented at 5500 × g for 5 min. The supernatant was discarded and the pellet was resuspended in 5 ml of salt medium. Protein was determined by the biuret method using bovine serum albumin (BSA) as a standard (8). The suspension was diluted to a final concentration of 2 mg protein/ml in salt medium and then 0.2 g BSA/100 ml (0.2%) was added.

Description of Respirometer

The respirometer consisted of a "flowboard" through which the flow of air could be accurately regulated (± 0.1 ml/min) for each of eight outlets. There were two separate manifolds, each with 4 outputs, thus allowing controls (air only) to be run side-by-side with synaptosomes being exposed to halothane. Halothane was introduced to the air stream with a Dräger Vapor 19 vaporizer. The gas streams were humidified by passage through bubble chambers filled with water before flowing through reaction vessels containing the synaptosomal mix that was immersed in a 32°C waterbath.

[Methyl-^{3}H]Choline Uptake

The synaptosomal suspension (5 ml, 2 mg protein/ml) was placed in each reaction vessel. Neostigmine (100 μM), antifoam spray (20 μl, AH Thomas Company, Philadelphia, PA), sodium pyruvate (5 mM) and [methyl-^{3}H]choline chloride (0.5-10 μM) were added to each reaction vessel. Air or halothane/air (vol/vol) was passed through the suspension at a flow rate of 2.5 ml/min. The synaptosomes were exposed to the air or halothane/air for 15 min before beginning the uptake studies. The vessels were then placed in an ice bath, and when the temperature of the suspension reached 4°C, 1 μCi of [methyl-^{3}H]choline chloride (80 Ci/mmol) was added. After 1 min, two 300-μl samples were removed from each vessel and added to 1 ml of ice-cold salt medium containing 200 μM choline chloride and immediately sedimented for 5 min in a refrigerated Eppendorf Centrifuge 5412. These samples were used as blanks. The vessels were then incubated in the 32°C water bath and the sampling procedure was repeated at designated intervals up to 90 min. After the samples were sedimented, the supernatant was removed and the pellet was rinsed with 1 ml of ice-cold salt medium. Lysing of the synaptosomal pellets was achieved by the addition of 0.25 ml of water to each pellet and pellets were stored overnight at 4°C. Then 4.0 ml Aquasol (New England Nuclear, Boston, MA) was added for liquid scintillation counting. Kinetic values for [methyl-^{3}H]choline uptake were determined using Lineweaver-Burk analysis. All statistical comparisons were made using Student's *t*-test for the means of two samples.

Choline Acetyltransferase Activity (ChAT)

ChAT activity was determined in the synaptosomes using a modification of the technique of Fonnum (9). Synaptosomes were suspended in an incubation medium containing 300 mM NaCl, 50 mM sodium phosphate, 20 mM EDTA, 1 mM neostigmine, and 0.5% Triton X-100, pH 7.4 at a concentration of 12 mg protein/ml. Then, 50 μl of a substrate mixture containing the incubation mixture without the Triton X-100 but with 2.1 mM [1-^{14}C]acetyl-CoA (35 mCi/mmol) and 16 mM choline-bromide was placed in small reaction vessels and exposed to air or 3 or 4% halothane/air (vol/vol) to equilibrate the solutions. After 10 min, 50 μl of the synaptosomal mixture was added to the substrate solution and the mixture was incubated for another 30 min. The mixture was then placed on ice and ^{14}C-ACh was extracted as described by Fonnum (9). The reaction rate was shown to be linear under these conditions for 60 min. Purified ChAT (Sigma Chemical Company, St. Louis, MO) was used as a standard during the procedure.

Acetylcholine Synthesis and Release

Depletion of synaptosomal Ach was achieved by preincubation in a high K^+ medium. The synapto-

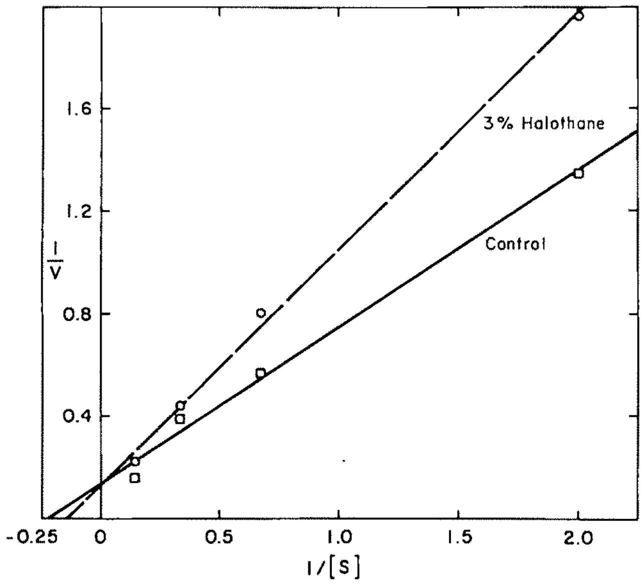

Figure 1. Lineweaver–Burk analysis of choline uptake. 3% halothane/air (vol/vol) does not cause a significant change in the V_{max} value, but does significantly increase the K_m value.

Table 1. The Effects of 4% Halothane on ChAT Activity

	Air	4% halothane/air (vol/vol)
Synaptosomal ChAT (n = 12) (cpm/mg protein)	1531 ± 64	1589 ± 62
Purified ChAT (n = 10) (cpm/0.25 U)	777 ± 54	737 ± 30

All values ± SEM.

somes were suspended in an ACh "depletion" medium containing 230 mM sucrose, 35 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, and 20 mM HEPES, pH 7.4 at a concentration of 2 mg protein/ml. This mixture was placed in the respirometer at 32° C for 10 min. At the end of the depletion period the synaptosomes were sedimented at 5500 × g for 5 min, resuspended in a synthesis medium containing 120 mM NaCl, 5 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, 20 mM HEPES, 5 mM sodium pyruvate, and 10 μM choline chloride, pH 7.4 at a concentration of 2 mg protein/ml, placed in the respirometer with 50 μl of antifoam, and exposed to either air or 3% halothane/air (vol/vol). At 0, 30, and 60 min, 200 μl samples were taken, placed in 500 μl of ice-cold salt medium and sedimented for 5 min in a refrigerated Eppendorf centrifuge. The pellets were rinsed twice with two volumes of ice-cold salt medium and then resuspended in 200 μl of salt medium with 0.5% Triton X-100 with or without 100 μM neostigmine and placed on ice. Acetylcholine levels were determined using the chemiluminescent technique of Israel and Lesbats (10). All measurements were made using an LKB Luminometer 1250. After the initial 60-min exposure to air or 3% halothane/air (vol/vol), the halothane was turned off and both of the synaptosomal mixtures were exposed to just air for another 30 min. At the end of this period, samples were taken and treated as described above. Total ACh levels in the synaptosomes were determined by subtracting the value determined for the sample with neostigmine from the value without neostigmine. ACh synthesis rate was calculated by subtracting the ACh level determined at 0 time from the total ACh level measured and dividing by the time.

To determine ACh release the synaptosomes were depolarized as described above and then placed in the synthesis medium for 1 hr. At the end of this period they were sedimented for 5 min at 5500 × g. The pellet was rinsed twice with salt medium and resuspended in a small volume of release medium that was the same as the synthesis medium but with the addition of 35 mM KCl, 100 μM neostigmine, and 20 μM hemicholinium-3. The suspension was then added to four volumes of depletion medium (that had been preequilibrated with air or 3% halothane/air in the respirometer) at a concentration of 2 mg protein/ml with 50 μl of antifoam. After 30 min, 200-μl samples were taken and immediately sedimented in a refrigerated Eppendorf centrifuge and ACh levels were measured in the supernatant as described above. The rate of ACh release was calculated by dividing the total ACh in the supernatant by 30 min.

Results

[Methyl-^{3}H]Choline Uptake

The apparent K_m for [methyl-^{3}H]choline uptake under control conditions (air only) was determined to be 4.69 ± 1.09 μM (n = 4) and the V_{max} was 9.97 ± 0.88 pmol·min^{-1}·mg^{-1} protein (n = 7). The determinations for choline uptake were made over the first 15 min. Halothane (3%) caused a significant increase ($P <$ 0.02) in the apparent K_m (10.44 ± 2.16 M, n = 4), but only a small increase in the V_{max} (12.89 ± 3.34 pmol·min^{-1}·mg^{-1} protein, n = 4). A Lineweaver-Burk plot of a typical experiment is shown in Figure 1.

Choline Acetyltransferase Activity

The level of ChAT activity in synaptosomes was determined to be 0.47 ± 0.2 nmol·min^{-1}·mg^{-1} protein (n = 4). Neither 3 nor 4% halothane (Table 1) had any effect on purified or synaptosomal ChAT. These

Table 2. The Effects of 3% Halothane on Acetylcholine Synthesis and Release

	Control (pmol·min^{-1}·mg^{-1} protein)	3% Halothane (pmol·min^{-1}·mg^{-1} protein)	% of control
ACh synthesis (n = 4)	18.00 ± 4.01	2.54 ± 1.47	14%
ACh release (n = 4)	19.57 ± 1.73	9.86 ± 2.27	50%

All values ± SEM.

results are not surprising since ChAT is not a primary factor in the regulation of ACh levels in the brain (11).

Acetylcholine Synthesis and Release

The rates for ACh synthesis and release were similar to those determined by other investigators in synaptosomes (12,13). Halothane (3%) greatly depressed both ACh synthesis ($P < 0.005$) and release ($P < 0.02$), although it had its greatest effect on ACh synthesis (Table 2). The depression of ACh synthesis by 3% halothane was completely reversible. If halothane-treated synaptosomes were exposed to air for 30 min, the ACh synthesis rates returned to normal levels (Table 3).

Discussion

Halothane is one of the most commonly used anesthetics. It depresses the central nervous system uniformly, does not induce electrocortical seizures, and depresses the sympathetic nervous system (6,14). Halothane also has a pronounced effect on ACh that plays an important role in the maintenance of consciousness (2). Halothane decreases the turnover of ACh in the brain (6), and inhibits the transfer of radioactivity from [2-^{14}C]pyruvate to ACh in brain slices (4). Since ACh is an important neurotransmitter involved in consciousness, it is important to understand the mechanisms underlying these observations. Ngai et al. (6) commented that more research needed to be done to determine whether the inhibition of ACh turnover and synthesis by halothane is due to an interference with choline transport, direct inhibition of ChAT, or altered energy metabolism.

We addressed these problems by studying the effects of halothane on ACh synthetic processes in synaptosomes. Synaptosomes include the presynapse, cleft, and postsynaptic components of brain synapses (15), and anesthetics are known to act on the central nervous system synapses (16). Synaptosomes are also able to carry on many of the processes that take place in nerve terminals in vivo (15) and maintain their integrity for over 8 hr under the appropriate conditions (Johnson and Hartzell, unpublished observations). Therefore, they are an excellent in vitro model system to study the effects of anesthetics.

Choline for acetylcholine synthesis is transported into cholinergic nerve terminals by a carrier-mediated system that has a high affinity for choline (17,18). Synaptosomes have been used extensively to study this process (19,20,21). We have demonstrated that halothane inhibits [methyl-^{3}H]choline uptake in synaptosomes. This inhibition of choline uptake by halothane appears to be "competitive-like" (Fig. 1). The K_m values were significantly different while the V_{max} values were not. On the other hand, ChAT activity was unaffected by halothane (Table 1). Since halothane significantly depressed ACh synthesis (Table 2), but did not affect ChAT, this would point to choline transport as being a site of action of halothane. This effect by halothane on choline uptake is compatible with the simple binding model of Franks and Lieb (22). This hypothesis states that, "general anesthetics act by binding directly to a particularly sensitive protein (which may or may not be membrane-bound) and inhibiting its normal function." It is therefore suggested that halothane inhibits ACh synthesis by directly interfering with the carrier-mediated transport system of choline. This interpretation of our results is also supported by Richards (16) who concluded, "it is more realistic to abandon a unitary theory of anesthetic action and postulate that the effects of an anesthetic at a particular site depend upon the precise structures of both anesthetic and binding site." It must also be noted that a given anesthetic probably does not bind to or act upon just a single protein. Rather, it is more likely that several proteins are sensitive to a particular anesthetic. Since halothane inhibits the release of ACh, as well as choline uptake, it is suggested that it is acting upon more than one site in cholinergic nerve endings.

In the synaptosomes, the effect of halothane on ACh synthesis is completely reversible (Table 3). After halothane is removed from the system, the rate of ACh synthesis returns to normal or slightly elevated levels. The ability of synaptosomes to "recover" from halothane exposure is an important characteristic of the model system.

The concept of an anesthetic inducing narcosis by binding to a specific sensitive protein(s) and thereby inhibiting normal function has just recently started to gain favor as the most likely mechanism for anesthetic

Table 3. The Effects of Removing Halothane from the System on the Rate of Acetylcholine Synthesis in Synaptosomes

	Initial 60 min	Additional 30 min of air only
Air	13.45 ± 2.07	10.38 ± 1.71
3% halothane	1.90 ± 0.73	17.48 ± 1.74

All values expressed as pmols ACh/min/mg protein ± SEM (n = 4). See text for further explanation.

action (16,22). Previous to this, "unitary" hypotheses were most popular. These theories suggest that anesthetics exert some "general" effect on the CNS and thereby induce narcosis (23,24,25). However, there is no effect on synaptic transmission that is common to all general anesthetics and all synapses (16). Also, many anomalies have been demonstrated in the "unitary" hypotheses. Therefore, there has been a move toward theories involving nonunitary molecular mechanisms of general anesthesia (26,27,28). Considering these facts, we propose that halothane inhibits ACh synthesis by interfering with the carrier-mediated choline transport system and also binds to other sensitive proteins inhibiting their normal function and it is the cumulative effect of specific interactions that depresses ACh synthesis.

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Negative Inotropic Effect of Etomidate in Rabbit Papillary Muscle

Hirochika Komai, PhD, Dawn E. DeWitt, BA, and Ben F. Rusy, MD

KOMAI H, DEWITT DE, RUSY BF. Negative inotropic effect of etomidate in rabbit papillary muscle. Anesth Analg 1985;64:400–4.

The effect of etomidate on the developed force of isometrically contracting rabbit papillary muscles in modified Krebs–Henseleit bicarbonate medium was evaluated under various stimulation conditions to gain insight into the mechanism underlying the negative inotropic effect of this anesthetic. Myocardial depressant effects of etomidate (2 and 4 mg/L) on steady-state contractions at low stimulation frequencies (0.1–0.5 Hz) were more pronounced than the effects on either steady-state contraction at high stimulation frequencies (1.0–2.0 Hz) or the effects on post-rest potentiated state contractions. Increases in the concentration of extracellular Ca^{2+} from an initial level of 2.5 mM to 3.4–4.0 mM reversed the effect of 2 mg/L of etomidate, whereas an increase to 4.6–5.0 mM was required to reverse the effect of 4 mg/L of etomidate. The dependence of post-rest potentiation on the duration of the preceding rest period was virtually unaffected by etomidate. These results suggest that etomidate inhibits the influx of extracellular Ca^{2+} but has little effect on the availability of intracellular Ca^{2+} required for the activation of myocardial contractile activity. Because the concentrations of etomidate required to produce negative inotropic responses in the present study are substantially greater than those likely to be achieved under clinical conditions, the present results also suggest that negative inotropism is unlikely in patients with normal hearts.

Key Words: ANESTHETICS, INTRAVENOUS—etomidate.

Although the intravenous general anesthetic etomidate has negative inotropic effects, these are considerably less than those of thiopental at equianesthetic concentrations (1). To gain insight into the mechanism underlying the negative inotropic effect of etomidate, we evaluated the effect of etomidate on the developed force of isometrically contracting rabbit papillary muscles under various stimulation conditions. An increase in stimulation frequency enhances myocardial developed force by increasing the influx of extracellular Ca^{2+} per unit time (2). This increase in force is not sensitive to the action of ryanodine, an inhibitor of sarcoplasmic reticulum function (3), and the sarcolemma has been proposed as the site of Ca^{2+} accumulation that accompanies an increase in stimulation frequency (4). In contrast, potentiated-state contractions appear to be determined largely by Ca^{2+} stored in and released from the sarcoplasmic reticulum, because they are sensitive to the action of ryanodine (4). Thus studying the effect of a drug on developed force under different stimulation conditions permits an assessment of the effect of the drug on the availability of extracellular and intracellular Ca^{2+}, both of which are involved in the activation of mammalian myocardial contractile activity (5).

Materials and Methods

Rabbits weighing about 2 kg ($n=13$) were anesthetized by intravenous injection of pentobarbital (approximately 45 mg/kg). A papillary muscle was isolated from the right ventricle of each heart. The muscle was mounted vertically in a tissue bath (45 ml) maintained at 30°C. The isometric forces of contraction and muscle dimensions were measured as described earlier (6). Muscle cross-sectional area (mean ± SD) was 0.66 ± 0.18 mm² ($n=13$). The muscles were field stimulated by a pair of silver field electrodes using an American Electronics Laboratory stimulator Model 104A. Stimuli 4-msec long and 1.5 times the threshold were used. The control medium was a modified Krebs–Henseleit bicarbonate of the following composition: NaCl, 115 mM; KCl, 5.9 mM; $MgCl_2$, 1.2 mM; NaH_2PO_4, 1.2 mM; Na_2SO_4, 1.2 mM; $NaHCO_3$, 25 mM; $CaCl_2$, 2.5 mM; and glucose, 5.6 mM. Ethylenediaminetetraacetate (EDTA), 50 μM, was added to chelate trace metals. The medium was equilibrated with a gas mixture of 95% O_2 and 5% CO_2. Small aliquots (up to 90 μl) of etomidate solution containing 35% (vol/vol) of propylene glycol were added

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Address correspondence to Dr. Komai, Department of Anesthesiology, Center for Health Sciences, University of Wisconsin, Madison, WI 53792.

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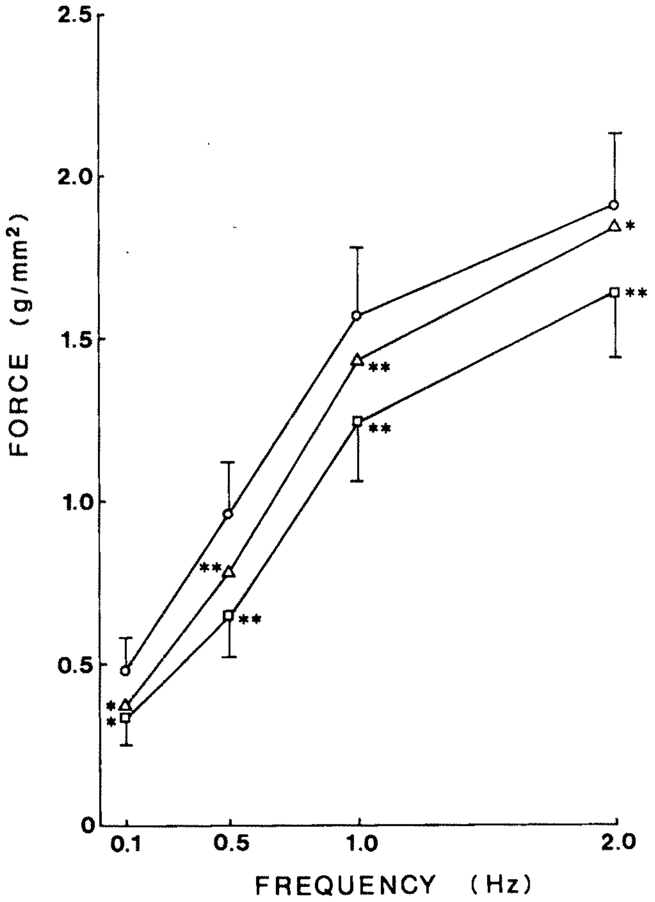

Figure 1. Negative inotropic effect of etomidate at different stimulation frequencies. Mean ± SEM ($n = 7$) are shown. (○), control; (△), etomidate 2 mg/L; (□), etomiate 4 mg/L. *$P < 0.05$, **$P < 0.01$, compared to corresponding control value (paired t-test).

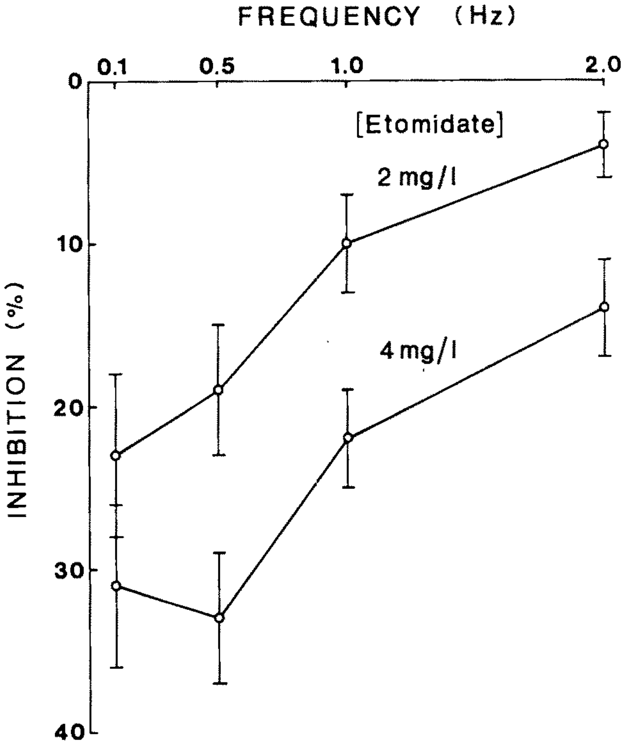

Figure 2. Frequency dependency of the negative inotropic effect of etomidate. Means ± SEM ($n = 7$) of % inhibition calculated for each muscle are shown. At both concentrations of etomidate, the % inhibition at 2.0 Hz was significantly ($P < 0.05$, Tukey's test) smaller than the % inhibition at 0.1 or 0.5 Hz.

to obtain the desired concentrations of the anesthetic (2 and 4 mg/L). Equivalent amounts of propylene glycol, without etomidate, were added to determine the effect of propylene glycol on the contractile activity of the muscle. After each change in the composition of the medium, contractile activity was measured after the force of contraction had stabilized (10–20 min). With seven muscles, the effects of etomidate on the force of steady-state contraction at various stimulation frequencies and the effects on the relationship between the force of potentiated-state contraction and pre-rest period were studied in the following order: control; etomidate 2 mg/L; etomidate 4 mg/L; and replacement of etomidate-containing medium by the control medium to test the reversibility of etomidate action. The reversal of the etomidate effect by increasing extracellular Ca^{2+} concentration was studied with six muscles in the following order: control, Ca^{2+} 2.5 mM, no etomidate; and etomidate 2 mg/L with a Ca^{2+} concentration of 2.5, 3.0, 4.0, and 5.0 mM. This was followed by replacement of the etomidate-containing medium by the control medium, etomidate 4 mg/L with a Ca^{2+} concentration of 2.5, 3.0, 4.0, and 5.0 mM. Potentiated-state contractions were elicited after a specified rest period after a steady-state at a stimulation frequency of 2.0 Hz (7). The effect of etomidate on the potentiated-state contraction elicited after a 2-sec interval was determined with all 13 muscles. Data were statistically evaluated by Student's t-test or by analysis of variance and Tukey's test (8).

Results

Etomidate (2–4 mg/L) had a small negative inotropic effect at all stimulation frequencies tested (Fig. 1). Although there was a variability in the developed force of individual muscles, the effects of etomidate were consistent and statistically significant ($P < 0.05$, paired t-test). The vehicle (propylene glycol) had no effect. The effect of etomidate on the force of contraction at 1.0–2.0 Hz was readily reversed (within 20 min) when the etomidate-containing medium was replaced by the control medium, but the effect on the force of contraction at 0.1–0.5 Hz was not completely

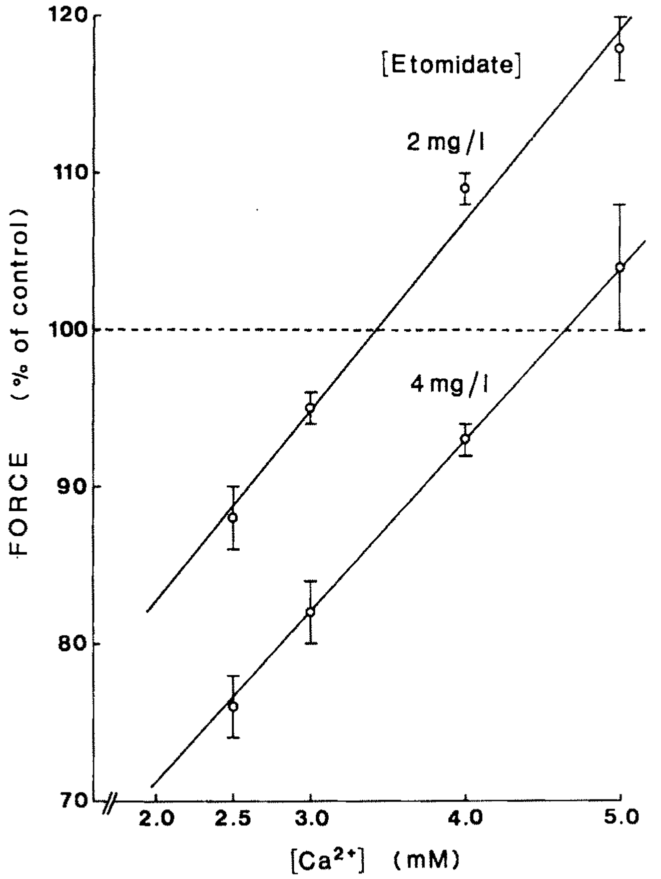

Figure 3. Reversal of the negative inotropic effect of etomidate by increase in Ca^{2+} concentration of the medium. Mean ± SEM (n = 6) of the developed force expressed as % of control (Ca^{2+} 2.5 mM, no etomidate) are shown. Linear regression lines were drawn through the experimental points (r = 0.9946 and 0.9999, both $P < 0.01$ for etomidate 2 mg/L and 4 mg/L, respectively). Control values of developed force were (mean ± SEM) 2.61 ± 0.26 g/mm² for etomidate 2 mg/L and 2.46 ± 0.26 g/mm² for etomidate 4 mg/L. Although these values are higher than those of Figure 1, in terms of % inhibition by etomidate (see Fig. 2), these two groups of muscles were very similar.

Table 1. Estimated Extracellular Ca^{2+} Concentration for the Reversal of Etomidate Effect

[Etomidate] (mg/L)	Stimulation frequency (Hz)	[Ca^{2+}] for reversal of etomidate effect[a]
2	0.1	3.7
	0.5	4.0
	1.0	3.4
	2.0	3.5
4	0.1	4.7
	0.5	4.8
	1.0	4.6
	2.0	5.0

[a] Estimated Ca^{2+} concentration for the force 100% of control in linear regression equations obtained from mean values of force (% of control, n = 6) at four different concentrations of extracellular Ca^{2+} (see Fig. 3 for an example at stimulation frequency of 1.0 Hz).

Table 2. Effect of Etomidate on Potentiated-State Contraction

Etomidate (mg/L)	Developed force (g/mm²)[a]	% Inhibition[b]
0	2.81 ± 0.27	(0)
2	2.66 ± 0.25[c]	5 ± 1
4	2.37 ± 0.21[c]	15 ± 2

[a] Mean ± SEM, (n = 13). [b] Mean ± SEM, (n = 13) of % inhibition for each muscle. [c] $P < 0.01$ compared to control (paired t-test).

reversed even 40 min after the replacement of the medium. Figure 2 shows the frequency dependence of inhibition by 2 and 4 mg/L of etomidate at increasing stimulation frequencies. The percent inhibition was significantly more pronounced at 0.1–0.5 Hz than at 2.0 Hz in the presence of both concentrations of etomidate ($P < 0.05$, analysis of variance and Tukey's test). An increase in the concentration of extracellular Ca^{2+} in the presence of etomidate increased the force of contraction linearly and, at sufficiently high concentration, reversed the negative inotropic effect of etomidate. Figure 3 illustrates the linear relationship between the force of contraction at a stimulation frequency of 1.0 Hz expressed as the percent of control value and the extracellular Ca^{2+} concentration. From the estimated Ca^{2+} concentrations (3.4 and 4.6 mM) at the points at which the linear regression lines intersect the 100% of control line, it can be seen that an increase in extracellular Ca^{2+} of 0.9 mM would be required to reverse the effect of 2 mg/L of etomidate and an increase of 2.1 mM would be required to reverse the effect of 4 mM of etomidate. Similar results were obtained at stimulation frequencies of 0.1, 0.5, and 2.0 Hz, with linear relationships having correlation coefficients greater than 0.95 ($P < 0.05$). Estimated concentrations of Ca^{2+} for the reversal of 2 mg/L of etomidate ranged from 3.4 to 4.0 mM (increase of 0.9–1.5 mM) and those for the reversal of 4 mg/L of etomidate, 4.6 to 5.0 mM (increase of 2.1–2.5 mM) for stimulation frequencies of 0.1–2.0 Hz (Table 1). To determine the effect of etomidate on the availability of intracellular Ca^{2+}, we measured the relationship between the force of post-rest potentiated-state contraction and the length of the pre-rest periods. As can be seen in Figure 4, etomidate did not change the shape of the force–rest curve, although there was a small change in the peak height. Table 2 illustrates that the effects of etomidate on potentiated-state contraction (measured at 2-sec rest period) were comparable to those of steady-state contraction at a stimulation frequency of 2.0 Hz (see Fig. 2).

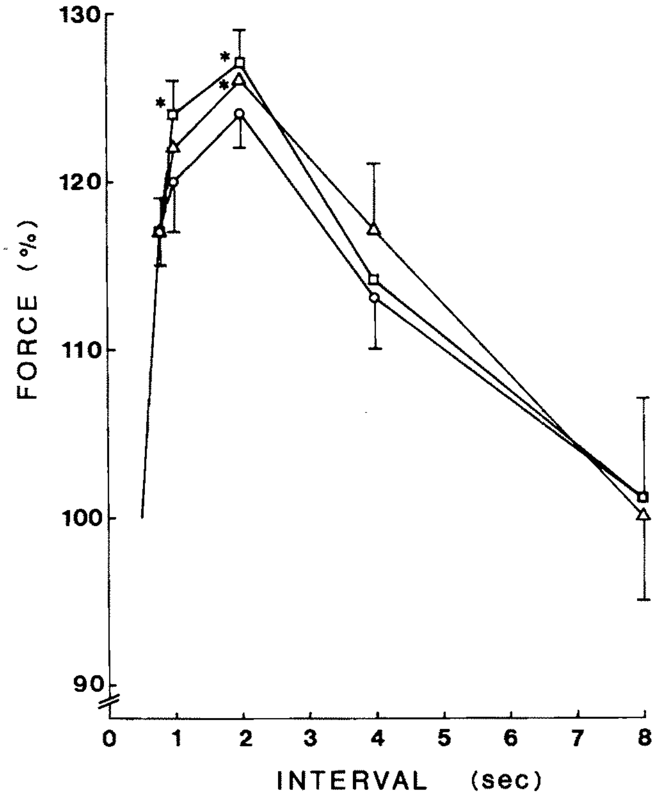

Figure 4. Effect of etomidate on the relationship between the force of potentiated-state contraction and the length of preceeding rest period. The force of potentiated-state contraction is expressed as percent of corresponding steady-state value at 2.0 Hz. Mean ± SEM (n = 7) are shown. (○), control; (△), etomidate 2 mg/L; (□), etomidate 4 mg/L. *$P < 0.05$ (paired t-test).

Discussion

The observed frequency dependence of the negative inotropic effect of etomidate resembles that of Ni^{2+}, La^{3+}, and low extracellular Ca^{2+} concentration (9) in that the effect is more pronounced at low than at high stimulation frequencies. In this regard, etomidate did not behave like the calcium channel blockers, verapamil and D600, which show a strong negative inotropic effect only at high stimulation frequencies (9). Among anesthetics and related drugs, diphenylhydatoin (10) shows a frequency dependence of negative inotropy similar to that of etomidate, whereas thiopental, methohexital, and ketamine (11) resemble calcium channel blockers in this regard. The effect of Ca^{2+} concentration of the medium on the myocardial depressant effect of etomidate suggests that etomidate may competitively inhibit the influx of extracellular Ca^{2-}. The effect of etomidate on potentiated-state contraction was similar to that on steady-state at high stimulation frequencies and much less than that on steady-state at low stimulation frequencies, suggesting that any condition that increases the influx of extracellular Ca^{2+} tends to reduce the etomidate effect. Unlike thiopental (7), etomidate had little effect on the force–rest relationship. This suggests that etomidate has little effect on the rate of intracellular transport of Ca^{2+} that is proposed by Edman and Jóhannsson (2) as an important determinant of the length of the rest period that precedes an optimal post-rest potentiated-state contraction. In conclusion, the results of the present study suggest that etomidate primarily inhibits the influx of extracellular Ca^{2+} and has little effect on the availability of intracellular Ca^{2+} for the activation of myocardial contractile activity.

The primary focus of the present study was the mechanism underlying the negative inotropic effect of etomidate. Even so, it is apparent from the results of the present study that the direct myocardial depressant effect of clinical doses of etomidate will be small. Total plasma concentrations of etomidate similar to those used in the present study (2–4 mg/L) may be attained briefly soon after injection of the induction dose of the anesthetic, but 4 min after injection of 0.3 mg/kg of etomidate, the plasma concentration is only about 0.3 mg/L (12). Because of protein binding of etomidate, however, the free etomidate concentration in plasma will be even lower than the total plasma concentration, and a free etomidate concentration equivalent to 2–4 mg/L in protein-free medium used in the present study is unlikely to be achieved clinically. Thus the negative inotropic effect of clinical doses of etomidate is expected to be much smaller than the effects observed in the present study, at least in patients with normal myocardial function, although the effect in patients with abnormal myocardial function may be greater.

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The Effect of Fluosol-DA on Induction of Inhalation Anesthesia

Robert T. Chilcoat, PhD, John I. Gerson, MD, Forrest B. Allen, MD, and
William W. Mapleson, DSc

CHILCOAT RT, GERSON JI, ALLEN FB, MAPLESON WW. The effect of Fluosol-DA on induction of inhalation anesthesia. Anesth Analg 1985;64:405–10.

The liquid/gas partition coefficients of three inhalation anesthetics in Fluosol-DA 20% (Fluosol), a perfluorocarbon blood substitute, were determined in vitro. The high values found (6.68 for halothane, 7.54 for enflurane, and 7.20 for isoflurane) suggested that induction with these agents would be prolonged in patients treated with Fluosol. Induction of isoflurane anesthesia (as a representative agent) at constant inspired concentration was studied in five mongrel dogs before and after replacement of about 25% of each animal's blood volume with Fluosol. Inspired and end-tidal isoflurane and carbon dioxide concentrations were recorded breath by breath, together with cardiac output. There was a significant delay in rise of end-tidal isoflurane concentration after Fluosol infusion. However, because cardiac output could not be held constant during each experiment, and because cardiac output also affects the rate of rise of alveolar anesthetic concentration, a physiological computer model was used to compare the isoflurane blood/gas partition coefficients that must have existed to account for the observed end-tidal levels before and after Fluosol infusion, while taking cardiac output variation into account. Post-Fluosol blood/gas partition coefficients calculated in this way (2.59 ± 0.51 SD) were significantly different ($P < 0.001$) from pre-Fluosol levels (1.45 ± 0.15 SD) and were not significantly different from post-Fluosol partition coefficients calculated by volume-weighted averaging (2.91 ± 0.36 SD). This indicates that the delay observed was attributable in large part to increased solubility of isoflurane in blood after addition of Fluosol. Based on their similar liquid/gas partition coefficients in Fluosol, similar delays should occur with halothane and enflurane.

Key Words: PHARMACOLOGY—Fluosol. SOLUBILITY—partition coefficients in Fluosol.

Fluosol-DA (Alpha Therapeutic Corporation, Los Angeles, CA) is an inert emulsion of two perfluorocarbons, perfluorodecalin and perfluorotripropylamine, that is being tested experimentally as a substitute for blood (1). The perfluorocarbons dissolve large quantities of oxygen and can markedly increase the oxygen-carrying capacity of hemoglobin-poor blood. Unlike hemoglobin, the perfluorocarbons dissolve oxygen linearly with PO_2 (i.e., obeying Henry's law). However, like hemoglobin, Fluosol-DA unloads its dissolved oxygen to the tissues, increasing oxygen delivery to tissues in anemic patients (1). Two preparations of Fluosol-DA are currently being tested, one containing 20% and the other 35% perfluorocarbons by weight, respectively. The more common of the two, Fluosol-DA 20% (Fluosol), was used throughout this study.

Because perfluorocarbons are immiscible with water, it was hypothesized that they would exhibit a relatively high affinity for the inhalation anesthetics, and that the liquid/gas partition coefficients of Fluosol and of Fluosol–blood mixtures would therefore be increased above that of blood alone. This would have the effect of slowing induction of inhalation anesthesia in patients having a significant percentage of Fluosol in their circulation. Because this might alter the clinical management of these patients, a study was instituted to determine the solubility of the three principal inhalation anesthetics in Fluosol, and to determine the effects on anesthetic uptake of significant concentrations of Fluosol in blood. Because all three anesthetics exhibited similar solubilities in Fluosol (see below), only isoflurane, as a representative agent, was used to study anesthetic induction in vivo.

Methods

Liquid/gas partition coefficients for halothane, enflurane, and isoflurane in Fluosol were determined as

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Address correspondence to Dr. Chilcoat, Department of Anesthesiology, Upstate Medical Center, 750 E. Adams Street, Syracuse, NY 13210.

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follows. A 500-ml spherical flask with three ground-glass necks was prepared by epoxying three-way nylon Luer stopcocks into two ground-glass connectors, inserting these connectors into the two outer necks and closing the third, central neck with a ground-glass stopper. Ground-glass surfaces were sealed with a thin film of glycerine, and the two outer (stopcock-carrying) connectors were clamped down with plastic adhesive tape. The precise gas volume of the flask was determined by weighing before and after filling with water.

Initially the flask was flushed with dry air containing about 5% CO_2 and a percentage of anesthetic equivalent to approximately 2 MAC. The flask was then sealed and immersed in a water bath until equilibrated to 37°C. Excess pressure was then released, and the anesthetic concentration was measured (see below).

Approximately 50 ml of Fluosol was then injected rapidly, while simultaneously venting the flask (through the second Luer stopcock) to expel the gas displaced by the liquid. The flask was then resealed and agitated continually in the water bath. Measurements of anesthetic concentrations in the gas phase were made at 7 min and at 14 min.

A quadrupole mass spectrometer (BOC Medishield, Harlow, Essex, England) was used for measuring anesthetic concentrations. This was tuned to a mass-number/charge ratio of 47 and the gain was set to give adequate readings at the expected concentrations. Unknown concentrations were then determined by sampling first from a standard jar and then immediately from the flask containing the unknown. In order to determine the amount of anesthetic lost from the flask due to sampling, the pressure in the flask was measured (by means of an aneroid manometer) before and after taking the sample. Standard jars for each anesthetic were prepared by the method of Allott et al. (2).

Liquid/gas partition coefficients (λ) for each gas were computed for each anesthetic agent using equation (9) given in the Appendix. Two determinations were made for each agent.

To determine whether the rise of the end-tidal concentration of an inhalation anesthetic is delayed because of the presence of Fluosol, five experiments were undertaken on mongrel dogs (22–24 kg). Each animal was first anesthetized with pentobarbital (30 mg/kg), paralyzed with metocurine (0.5 mg/kg), intubated, and ventilated with air through a standard circle system using a Ventimeter ventilator (Air-Shields, Hatboro, PA). A 16-gauge intravenous cannula was placed in a femoral vein and a 14-French catheter into a femoral artery. Sampling capillaries for two LB-2 infrared gas analyzers (Beckman Instruments, Schiller, IL), calibrated for CO_2 and isoflurane, respectively, were placed down the endotracheal tube. A 7.5-French pulmonary-artery catheter was placed through a jugular vein for cardiac output measurements. Ventilation rate and tidal volume were adjusted until a stable end-tidal CO_2 concentration of 5% was achieved (approximately 2 hr after pentobarbital and metocurine). Body temperature was maintained constant by adjusting room temperature and by heating and humidifying inspired gases.

Isoflurane was then added to the breathing mixture for 20 min by manually adjusting a vaporizer to achieve rapidly and then maintain an inspired concentration of isoflurane (as measured on the infrared analyzer) at 1%. Breath-by-breath inspired and end-tidal levels were recorded to produce an uptake curve. Cardiac output was measured at 10-min intervals.

At the end of this inhalation induction, isoflurane was then washed out for at least 2 hr (to an end-tidal level of below 0.05%) using a nonrebreathing circuit. The circle breathing system was also purged of isoflurane. Supplemental doses (half the original) of pentobarbital and metocurine were then given. During this washout period, 750 ml of blood was removed rapidly (in less than 2 min) via the catheter in the femoral artery. The blood removed was immediately replaced by 1000 ml of Fluosol. The fluorocrit, a method of expressing the volume percentage of circulating perfluorocarbons, analogous to hematocrit, was measured. Cardiac output was reduced toward pre-Fluosol levels with propranolol (7–10 mg), verapamil (10–15 mg), or both, in four dogs. After ventilation was readjusted again to achieve a stable end-tidal CO_2 concentration of 5%, a second inhalation induction was performed.

Because an increase in cardiac output also delays the rise of alveolar tension during induction of inhalation anesthesia, and because cardiac output was never reduced exactly to pre-Fluosol levels, it was not possible to compare directly the pre- and post-Fluosol uptake curves. Therefore, the results were analyzed in such a way as to nullify the effect of any variation in cardiac output. To do this, a physiological computer model of anesthetic uptake was given the measurements of inspired isoflurane concentration and cardiac output. An iterative process was then employed to determine what value of the blood/gas partition coefficient (λ_B) used in the model produced the lowest mean squared error between the measured values of end-tidal isoflurane and those predicted from the model. A comparison of pre- and post-Fluosol λ_B

values calculated in this way was then made using the analysis of variance to determine whether they were significantly different.

The model used was essentially Mapleson's model "P" (3) as modified by Chilcoat (4,5) to permit long cardiac computation cycles. The model was translated into BASIC from the original FORTRAN IV version and computations were performed on an Apple II+ microcomputer (Apple Computers Inc, Cupertino, CA).

To determine pre- and post-Fluosol λ_B values for each experiment, the model was partly quantified with standard dog data (4,5), scaled for body mass. Then, for each set of experimental data, a trial value of λ_B was determined and this value used for additional quantification of the model. Final model quantification was provided breath by breath: for each breath the measured inspired concentration of isoflurane was given to the model, along with a value of cardiac output calculated by linear interpolation of the 10-min cardiac output measurements made during the experiment. The model's arterial tension for that breath was then calculated, and the difference between this and the corresponding measured end-tidal tension (corrected to arterial tension by assuming a "normal" arterial/end-tidal ratio (4,5) of 0.9) was calculated. These differences were squared and summed over the 13 min of the experiment, providing a residual sum of squares for that particular trial value of λ_B. New trial values were then selected (using a simple minimum-converging algorithm) and tried until the value of λ_B that minimized this residual sum of squares was found. The standard error of the estimate (6) was calculated for each optimum λ_B as the square root of the quantity: residual sum of squares divided by two less than the number of data points.

Results

The Fluosol/gas partition coefficient for the three volatile anesthetics is about seven. Table 1 gives liquid/gas partition coefficients for each determination, together with mean values for each agent. Accepted values of the blood/gas partition coefficient (7) are given for comparison. Also given for each determination are the partial pressure of the anesthetic and the total pressure in the flask at equilibrium.

The time for the end-tidal concentration of isoflurane to reach a given level in the animal experiments was significantly greater after Fluosol infusion. Table 2 shows this effect for two specific F_A/F_I ratios. Figure 1 is a composite graph of F_A/F_I vs time for all five dogs. Shown are mean values with vertical bars indicating ±1 SD. Because of slight differences in respiratory rate in each experiment, individual breaths were offset in time, and thus could not be directly averaged. Linear interpolation between breaths was used to estimate data values at specific times for averaging.

Table 1. Liquid/Gas Partition Coefficients (λ) for Three Anesthetics in Fluosol

Agent	λ	Partial pressure at equilibrium (mm Hg)	Total pressure at equilibrium (mm Hg)	λ_B[a]
Halothane	6.71	6.5	763.9	
	6.64	6.5	766.6	
Mean	6.68			2.3
Enflurane	7.77	10.7	756.8	
	7.32	12.4	762.8	
Mean	7.54			1.78
Isoflurane	7.27	8.0	762.8	
	7.14	8.4	756.1	
Mean	7.20			1.41

[a] Accepted values (7) of blood/gas partition coefficients (λ_B) are given for comparison.

The mean cardiac output at the start of the pre-Fluosol inductions was 3.65 ± 0.35 (SD) L/min. Cardiac output increased to 8.23 ± 0.69 (SD) L/min immediately after blood removal and Fluosol infusion. In the four dogs in which an attempt was made to restore cardiac output to baseline, the mean cardiac output was 3.96 ± 0.83 (SD) L/min immediately prior to the post-Fluosol induction (the value in the remaining dog stayed at 9.2).

The results of the computation of λ_B values by model fitting are presented in Table 3. The values in parentheses next to each value are the standard errors of the estimate (see Methods), which give an indication of the accuracy with which the model fit the experimental data for each determination. Also shown for comparison are post-Fluosol λ_B values calculated by volume-weighted averaging using the pre-Fluosol λ_B values and the percentages of Fluosol in each dog's circulation calculated from fluorocrits. Post-Fluosol λ_B values were significantly greater ($P < 0.001$ by analysis of variance); the mean value calculated by computer modelling was 2.59 ± 0.51 (SD) vs 1.45 ± 0.15 (SD) pre-Fluosol. In addition, post-Fluosol λ_B values predicted by volume-weighted averaging, mean 2.91 ± 0.36 (SD), were not significantly different from those calculated by model fitting.

Discussion

Our in vitro results show that Fluosol does indeed have a high affinity for the volatile anesthetics. The

Table 2. Times (min) to Reach Specific F_A/F_I Ratios before and after Administration of Fluosol

	Pre-Fluosol			Post-Fluosol[a]		
Dog no.	0.4	0.6	(F_A/F_I)	0.4	0.6	Fct[b]
1	0.56	2.00		1.58	9.02	3.1
2	0.37	2.09		0.96	7.21	4.1
3	0.29	1.04		0.51	2.76	3.3
4	0.30	1.64		0.61	5.00	4.3
5	0.42	1.51		0.69	3.88	4.8
Mean	0.39	1.66		0.87	5.57	
SD	0.11	0.42		0.43	2.53	

[a] Post-Fluosol values are significantly greater than pre-Fluosol values at the 0.0025 level by the two-factor analysis of variance (6).
[b] Fluorocrit after administration of Fluosol.

Fluosol/gas partition coefficient for all three agents is approximately seven. These values are similar to the values obtained by Tremper et al. (8), but are not identical. (Direct statistical comparison is not possible without the original data because of heterogeneity of variances (9).) If there is a difference, it is likely to be a result of differences in methods for measurement of partition coefficients.

Regardless of any discrepancy between our in-vitro results and those of Tremper et al., it is clear from both studies that the partition coefficients of inhalation anesthetics in Fluosol are much higher than those in blood. Therefore, at clinically useful concentrations of Fluosol (i.e., 20–25% of total circulating volume), a significant delay in induction of inhalation anesthesia should occur. Because the λ values for all three anesthetics are roughly the same, the largest effect will occur with the agent having the lowest blood/gas partition coefficient, i.e., isoflurane.

The anticipated effect of Fluosol on the rate of induction is confirmed by the in vivo results using isoflurane. Table 2 shows that the time taken for the alveolar (F_A)/inspired (F_I) isoflurane ratio to reach two representative levels increased significantly after Fluosol. Figure 1 shows mean F_A/F_I ratios in our five animals, plotted against time, before and after Fluosol infusion. It is clear from this figure that induction was delayed after Fluosol. Although this finding appears to confirm the theoretical prediction, the pre- and post-Fluosol curves should not be compared directly because of differences in cardiac output.

The rapid removal of 750 ml of blood and replacement with Fluosol approximately doubled cardiac output. Even after attempted adjustment with propranolol and verapamil in the last four dogs, a mean increase in cardiac output in all dogs of 25% ± 33% (SD) remained immediately prior to the post-Fluosol isoflurane inhalation. Because the data in Table 2 and Figure 1 are influenced by this increase in cardiac output, it is necessary to examine the results shown in Table 3 to determine whether the observed delay in the rise of end-tidal isoflurane concentration can be attributed to an increase in λ_B due to the presence of Fluosol.

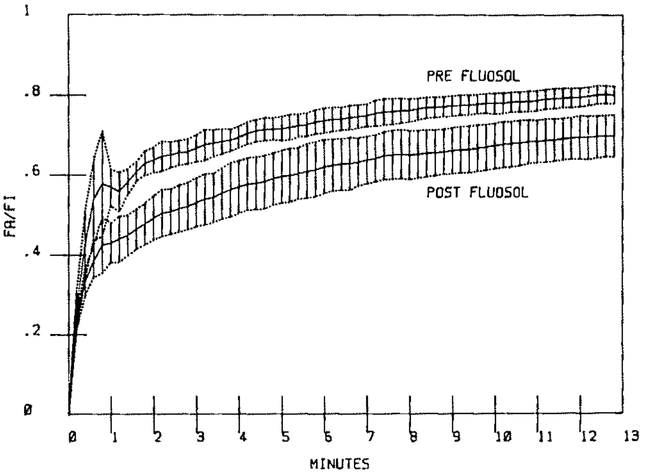

Figure 1. Alveolar(F_A)–Inspired(F_I) ratios during induction of 1% isoflurane anesthesia before and after administration of Fluosol. Means of five experiments ± 1 SD.

This appears to be the case. Using the randomized block analysis of variance (6,9), there is no significant difference between dogs. Furthermore, the post-Fluosol λ_B values are significantly greater than the pre-Fluosol λ_B values, indicating that even after variation in cardiac output before and after Fluosol infusion is taken into account, the remaining delay requires a significant increase in λ_B to account for the observed end-tidal concentrations. Post-Fluosol λ_B values could not be measured directly for comparison because the necessary equipment was not available for the animal experiments.

The fact that the mean value of the pre-Fluosol λ_B values is close to the generally accepted human value

Table 3. Values of Blood/Gas Partition Coefficients (λ_B) for Isoflurane Calculated by Best Fit of a Physiological Model to the Experimental Data

Dog no.	Pre-Fluosol λ_B	Post-Fluosol λ_B	%Fluosol[a]	Predicted post-Fluosol λ_B (weighted average)[c]
1	1.29 (0.015)[b]	2.16 (0.021)[b]	20%	2.47
2	1.58 (0.020)	2.97 (0.023)	27%	3.10
3	1.28 (0.011)	2.29 (0.030)	22%	2.58
4	1.55 (0.032)	3.28 (0.025)	28%	3.13
5	1.53 (0.016)	2.23 (0.016)	31%	3.29
Mean ± SD	1.45 ± 0.15	2.59 ± 0.51	25.6% ± 4.5%	2.91 ± 0.36[d]

[a] Calculated from fluorocrit.

[b] Standard error of the estimate (see text).

[c] Weighted average using pre-Fluosol λ_B values above, %Fluosol, and the measured Fluosol/gas partition coefficient for isoflurane from Table 1.

[d] From the analysis of variance, variability among dogs was not significant; variability among the three types of λ_B was highly significant ($P < 0.001$); orthogonal comparison (8) of the pre-Fluosol λ_B values with the two post-Fluosol λ_B values was highly significant ($P < 0.001$); orthogonal comparison between the two post-Fluosol λ_B values was not significant.

of 1.40 (7) is gratifying, but may be misleading. For fitting of the model to the experimental data, alveolar ventilation was assumed to be "normal" at 4 L/min. While this is justified on the grounds that end-tidal P_{CO_2} was kept constant at a fixed, normal level, a small variation in alveolar ventilation can have a significant effect on the value of λ_B computed by fitting the model to the experimental data. On the other hand, the fact that the post-Fluosol λ_B values computed by volume-weighted averaging were not significantly different from those calculated by model fitting indicates that alveolar ventilation did not vary significantly within each dog, and the low standard deviation (10%) on the pre-Fluosol λ_B values indicates low variability between dogs.

Fluosol delays induction with inhaled anesthetics in several ways. To be effective as an increaser of oxygen-carrying capacity, Fluosol must comprise a significant portion of the total blood volume and must be used in conjunction with inspired oxygen concentrations approaching 100%, precluding the use of nitrous oxide during anesthesia. The former requirement means that major increases in blood/gas partition coefficient, with concomitant delays in induction, will occur. The latter requirement can further delay induction by eliminating the second-gas effect (10). Furthermore, in this animal study, a large increase in cardiac output invariably occurred after Fluosol infusion. The cause of this is not clear, but a 33% increase in cardiac index after infusion of 500 ml of Fluosol has been reported in humans (11). Because Fluosol does cause an increase in cardiac output in humans, induction will also be delayed because of this. Similar delays will be seen on emergence.

The result of these several effects will be that to the anesthesiologist unaware that induction will be delayed in comparison with his usual experience, the patient may appear resistant to the anesthetic. The anesthesiologist may then increase the inspired concentration of the anesthetic in an attempt to compensate, rendering the patient unnecessarily deeply anesthetized as the delayed induction proceeds.

Fluosol provides a means of expanding circulating volume and increasing oxygen transport, without the need for crossmatching and without risk of disease transmission. If approved for general use, Fluosol will be used in patients coming to surgery for emergency operations and in patients having elective operations in whom crossmatching problems or religious beliefs preclude the use of blood and blood products. The anesthesiologist must be aware of the effects Fluosol will have on patients, so that their clinical management can be modified appropriately.

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Appendix

Computation of Liquid/Gas Partition Coefficient

The output of the mass spectrometer is proportional to the partial pressure of the anesthetic vapor at the tip of the sampling capillary. Assuming that the vapor behaves as an ideal gas at the concentrations encountered, partial pressure in a rigid container is given by

$$P = K\,L\,T$$

where K is a constant that includes the volume of the container, the molecular weight of the vapor, and the universal gas constant; L is the concentration (in g of anesthetic/L of gas) in the container and T is the absolute temperature. If the mass spectrometer gives a reading R_f from the equilibration flask and R_s from the standard jar,

$$\frac{R_f}{R_s} = \frac{K_f L_f T_f}{K_s L_s T_s}.$$

Because the temperature of the flask is held constant, and variation in temperature in the standard jar will be trivial, the K values and T values can be combined into one constant K'. Therefore, the concentration (g/L) in the equilibration flask is given by

$$L_f = K' L_s \frac{R_f}{R_s}. \tag{1}$$

If V_f is the volume of the flask, then after a volume V_L of liquid (Fluosol) is added, but before any anesthetic has been taken up by the liquid, the mass of anesthetic in the gas (M_{go}) is given by

$$M_{go} = (V_f - V_L)L_{fo} \tag{2}$$

where L_{fo} is the concentration in the flask at that time.

After equilibration, the mass of anesthetic present in the gas phase will be

$$M_{g\infty} = (V_f - V_L)L_{f\infty} \tag{3}$$

where $L_{f\infty}$ is the concentration remaining in the flask.

A small amount of anesthetic will be lost from the flask each time a measurement is made with the mass spectrometer. This will be given by

$$M_i = V_{si} L_{fi} \tag{4}$$

where V_{si} is the volume removed in the measurement sample and L_{fi} is the concentration of the sample.

In addition, a small loss occurs due to leakage and absorption. This can be determined approximately by doing a "dummy" equilibration without injection of Fluosol. If the fraction of anesthetic lost in this experiment is given by F_{leak}, the mass of anesthetic lost in an actual equilibration will be approximately

$$M_{\text{leak}} = V_f L_{f\infty} F_{\text{leak}}. \tag{5}$$

($L_{f\infty}$ is used here because the concentration will be closer to this level for most of the time during the equilibration.)

At the end of equilibration, the mass of anesthetic present in the liquid will be

$$M_L = M_{go} - M_{g\infty} - \sum_{i=1}^{n} M_i - M_{\text{leak}}. \tag{6}$$

The liquid/gas partition coefficient, λ, will be given by

$$\lambda = \frac{M_L/V_L}{M_{g\infty}/(V_f - V_L)}. \tag{7}$$

Substituting equations (2), (3), (4), (5), and (6) into equation (7),

$$\lambda = \frac{(V_f - V_L)(L_{fo} - L_{f\infty}) - \sum_{i=1}^{n} V_{si}L_{fi} - V_f L_{f\infty} F_{\text{leak}}}{V_L L_{f\infty}}. \tag{8}$$

Equation (1) can be substituted for each L_f. Because every term contains an L_f, the constant K' and L_s, the concentration of the standard, cancel. Equation (8) then becomes

$$\lambda = \frac{(V_f - V_L)\left(\dfrac{R_{fo}}{R_{so}} - \dfrac{R_{f\infty}}{R_{s\infty}}\right) - \sum_{i=1}^{n} V_{si}\dfrac{R_{fi}}{R_{si}} - V_f \dfrac{R_{f\infty}}{R_{s\infty}} F_{\text{leak}}}{V_L \dfrac{R_{f\infty}}{R_{s\infty}}}. \tag{9}$$

Vecuronium Infusion Dose Requirements during Fentanyl and Halothane Anesthesia in Humans

J. Swen, MD, Peter J. Gencarelli, MD, and H. W. J. Koot

SWEN J, GENCARELLI PJ, KOOT HWJ. Vecuronium infusion dose requirements during fentanyl and halothane anesthesia in humans. Anesth Analg 1985;64:411–4.

Steady-state infusion rate requirements of vecuronium were determined in 29 patients during either halothane–nitrous oxide or fentanyl–nitrous oxide anesthesia at different levels of neuromuscular block. During N_2O–halothane anesthesia (end-tidal concentration, 0.5%), the infusion rate necessary for a steady-state (defined as unchanging twitch height and infusion rate for at least 20 min) 50% depression of twitch force was 28.8 ± 5.4 (mean ± SD) ($n = 8$) and 47.6 ± 9.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($n = 6$) at 90% reduction of twitch force. During N_2O–fentanyl anesthesia, the steady-state infusion rate required for 50 and 90% decrease of twitch force was 56.3 ± 20.0 ($n = 9$) and 74.8 ± 16.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($n = 6$), respectively. The variances of vecuronium steady-state infusion dose requirements were smaller in the halothane groups than in the fentanyl anesthesia groups. The steady-state vecuronium infusion dose requirements during fentanyl anesthesia were greater than the mean infusion dose requirements during halothane anesthesia at equivalent levels of twitch depression.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium.

The new nondepolarizing muscle relaxant vecuronium (ORG NC 45) has a short elimination half-life, rapid clearance from plasma, and a correspondingly short duration of neuromuscular blockade (1). It has therefore been suggested that vecuronium be administered in continuous infusions for longer operations (2,3). There have been no reports in the literature of vecuronium infusion rates required for different levels of neuromuscular block or with different anesthetic techniques. Therefore, in normal patients, we measured and compared the vecuronium infusion rates necessary to achieve approximately 50 and 90% twitch force depression during fentanyl–nitrous oxide and halothane–nitrous oxide anesthesia.

Methods

Twenty-nine adult surgical patients without renal, hepatic, or neuromuscular disease (ASA class I or II) were studied. Each granted consent for participation in the research, which was approved by the University of Leiden Medical Ethics Committee. All patients were undergoing elective otolaryngologic surgical procedures: their mean (± SD) age was 37.2 yr (± 14.4) and weight 71.4 kg (± 13.9). Each patient was studied only once.

We randomly divided the patients into four groups. In groups A and B, patients were premedicated with atropine (0.5 mg), fentanyl (0.1 mg), and droperidol (5 mg intramuscularly) about 45 min before induction. Anesthesia was induced with thiopental (3–5 $mg \cdot kg^{-1}$) and fentanyl (0.1 mg intravenously) while the patients breathed 60% nitrous oxide in oxygen. Ventilation was assisted by mask to maintain normocarbia (measured by a Datascope 500 end-tidal CO_2 monitor). After obtaining a control twitch measurement, succinylcholine (0.5 $mg \cdot kg^{-1}$) was administered and the patients' tracheas were sprayed with lidocaine and intubated. Anesthesia was maintained with intravenous fentanyl (3–8 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) and 60% nitrous oxide in oxygen. After full recovery of twitch to control height, a bolus of vecuronium was administered and a continuous infusion started and adjusted to obtain a steady-state twitch depression (defined as unchanging infusion rate and twitch height for at least 20 min) of 50% in group A (nine patients) and 90% of control twitch tension in group B (six patients). In groups C and D, 14 patients were premedicated with diazepam (10 mg orally) 1 hr before induction of anesthesia. Anesthesia was begun with thiopental (2–5 $mg \cdot kg^{-1}$) and continued with 2% halothane and 60% nitrous oxide in oxygen. After spraying the trachea

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Address correspondence to Dr. Swen, Anesthesiologie, AZL, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands.

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Table 1. Steady State Characteristics

Steady state	Patient groups A	B	C	D
Mean (± SD) time from initial vecuronium bolus to beginning of steady state (min)	48.0 ± 17.4	41.3 ± 11.8	43.0 ± 15.1	38.5 ± 13.2
Mean (± SD) twitch depression (% control)	57.4 ± 9.9	89.0 ± 2.0	54.4 ± 3.8	91.9 ± 2.1

with lidocaine, intubation was accomplished without the administration of muscle relaxants. After intubation the halothane end-tidal concentration was reduced to 0.5% (as measured by a hydrogen flame ionization detector technique (4,5)) and maintained at this level for the remainder of the study. After a control twitch force measurement was obtained, an intravenous bolus of vecuronium (20 $\mu g \cdot kg^{-1}$) was administered and a continuous vecuronium infusion was begun. The rate of vecuronium infusion was adjusted to obtain a steady-state reduction of twitch force of 50% in group C (eight patients) and 90% in group D (six patients).

Neuromuscular function was monitored with a Grass S-88 nerve stimulator that applied square wave pulses at 0.1 Hz and 0.2-msec duration to 23-gauge steel needle electrodes placed near the ulnar nerve at the wrist. Force of thumb adduction was measured by a Statham UC-3 transducer with a 9-kg load cell and continuously recorded on a polygraph. Control twitch tension was established before any muscle relaxant was administered. End-tidal P_{CO_2} and esophageal temperature were monitored and kept within normal ranges.

The four groups were compared using analysis of variance and the group variances were compared with the variance ratio test (6). Statistically significant differences were assumed at $P < 0.05$.

Results

Patients of all groups were similar with respect to age and weight. For all four groups, the intended levels of twitch depression and those achieved at steady state, and the times from initial vecuronium bolus to the beginning of steady-state vecuronium infusion were not significantly different (Table 1).

At equivalent levels of twitch depression, the required steady-state vecuronium infusion dose was less in the group with halothane–nitrous oxide than in the group with fentanyl–nitrous oxide anesthesia. With halothane–nitrous oxide anesthesia, the steady-state infusion doses of vecuronium were greater at 90% (group D) than at 50% (group C) twitch height depression, whereas during fentanyl–nitrous oxide anesthesia there was no significant difference in the required vecuronium infusion doses at steady state at 90% (group B) and 50% (group A) twitch depression (Table 2). The variances of the required steady-state vecuronium infusion doses of the halothane–nitrous oxide anesthesia groups were significantly less than those of the fentanyl–nitrous oxide groups.

Discussion

Our data indicate two important differences in the required vecuronium infusion doses at steady state with fentanyl–nitrous oxide and with halothane–nitrous oxide anesthesia. First, at equivalent levels of twitch force depression, the steady-state vecuronium infusion doses were less during halothane–nitrous oxide than during fentanyl–nitrous oxide anesthesia. This result is consistent with previous research indicating that potent inhaled anesthetics augment the neuromuscular blockade from nondepolarizing muscle relaxants and that halothane anesthesia potentiates these relaxants more than nitrous oxide–narcotic anesthesia (7). Using vecuronium continuous infusions during both fentanyl–nitrous oxide and later halothane–nitrous oxide anesthesia in the same patients, Foldes et al. (8) reported that the dose of vecuronium required to produce approximately 90% steady-state block was 25–30% less during halothane (0.5% administered concentration) than during fentanyl anesthesia. Even though Foldes et al. measured this effect in only two patients, their results are similar to ours (in which the infusion dose during halothane–nitrous oxide anesthesia was 36% less than that during fentanyl–nitrous oxide anesthesia at 90% twitch depression). Stanski et al. (9) using the calculated steady-state serum level of relaxant required for 50% twitch force depression called the $Cpss_{50}$, reported patient sensitivity to *d*-tubocurarine increased by a factor of 1.7 during halothane (end-tidal concentration 0.5%)–nitrous oxide morphine–nitrous oxide anesthesia even though *d*-tubocurarine pharmacokinetics did not change. Interestingly, this value is close to 1.9, the ratio of mean vecuronium infusion doses re-

Table 2. Steady State Infusion Doses of Vecuronium

Level of twitch depression	Mean (± SD) vecuronium infusion dose at steady state ($\mu g \cdot kg^{-1} \cdot hr^{-1}$)	
	Fentanyl–N_2O anesthesia	Halothane–N_2O anesthesia
50%	56.3 ± 20.0 (group A)	28.8 ± 5.4 (group C)
90%	74.8 ± 16.0 (group B)	47.6 ± 9.7 (group D)

quired to produce a steady-state 50% twitch depression during fentanyl–nitrous oxide and halothane–nitrous oxide anesthesia in this study. By increasing halothane end-tidal concentration from 0.44 to 1.20%, Rupp et al. (10) reported that vecuronium neuromuscular block was not significantly enhanced. His results do not contradict our findings because Rupp et al. compared vecuronium potentiation at different halothane concentrations and our study compared vecuronium dose requirements during fentanyl and halothane anesthesia.

The second important difference in required vecuronium infusion doses for steady-state twitch depression during halothane–nitrous oxide and fentanyl–nitrous oxide anesthesia is that the variances were smaller with halothane than with fentanyl anesthesia. The reduction of variance in patient response to nondepolarizing muscle relaxants by halothane when compared to narcotic–nitrous oxide anesthesia has not been reported with most techniques of determining muscle relaxant dose–response data. But by using a method attempting to correlate relaxant serum concentration with twitch depression, Stanski et al. (9) reported a reduction in the variances of patient sensitivity to *d*-tubocurarine (measured as the $Cpss_{50}$) during halothane–nitrous oxide compared to morphine–nitrous oxide anesthesia.

The relatively large variation in vecuronium infusion dose requirements during fentanyl–nitrous oxide anesthesia observed in our study has been reported previously. Agoston et al. (3) described that the steady-state infusion dose of vecuronium required for 90% neuromuscular block during fentanyl–nitrous oxide anesthesia in nine patients ranged from 11 to 87 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. All of the infusion rates measured in our study in patients at the same level of twitch depression receiving the same type of anesthesia (group B) were within this range. The wide variation in vecuronium infusion doses required for steady state during fentanyl–nitrous oxide anesthesia and the relatively small numbers of patients in our study contributed to the absence of a statistically significant difference between groups A and B (50 and 90% block with fentanyl–nitrous oxide anesthesia).

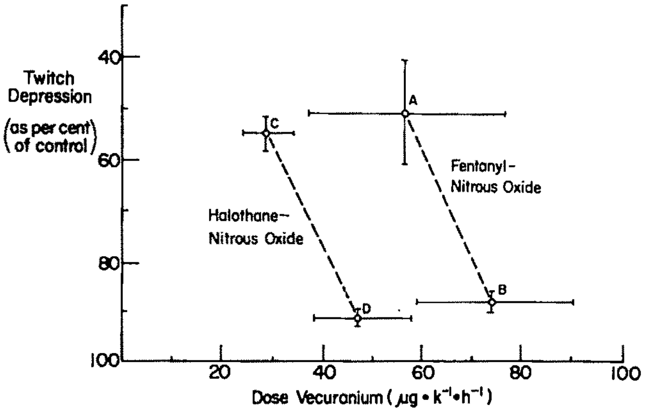

Figure 1. Comparison of steady-state vecuronium infusion doses and percentage twitch depression during fentanyl–nitrous oxide and during halothane–nitrous oxide anesthesia. Circles (and lines) represent mean (± SD) infusion doses and twitch depression for each study group. Broken lines connect the groups with the same anesthetic and are added to aid interpretation.

It is possible that the succinylcholine used in groups A and B altered vecuronium pharmacokinetics or pharmacodynamics. d'Hollander et al. (11) found vecuronium duration of effect prolonged and dose–response increased for up to 30 min after twitch depression had returned to normal after succinylcholine (1.0 $mg \cdot kg^{-1}$) during fentanyl–nitrous oxide anesthesia. But Fisher and Miller (12) showed that during halothane anesthesia the vecuronium peak effect, onset, duration of action, and recovery times at 5 and 60 min after succinylcholine (0.5 $mg \cdot kg^{-1}$) were unchanged from control measurements made without succinylcholine. An effect from 0.5 $mg \cdot kg^{-1}$ succinylcholine on subsequent vecuronium neuromuscular blockade during fentanyl–nitrous oxide anesthesia is possible but heretofore undescribed.

According to pharmacokinetic theory, during a steady state the plasma concentration of drug (Css), constant rate of infusion (R), and drug clearance (Cl) are related by the following formula (13): $Css = R/Cl$. Cronnelly et al. (1) simultaneously measured the pharmacokinetics and pharmacodynamics of vecuronium during halothane (end-tidal concentration 0.5–0.7%)–nitrous oxide anesthesia and calculated the clearance of vecuronium to be 5.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and the $Cpss_{50}$ to be 54 $ng \cdot ml^{-1}$. With the use of these figures in the above formula solved for infusion rate, the calculated constant vecuronium infusion rate necessary for 50% neuromuscular blockade is 29.3 $mg \cdot kg^{-1} \cdot hr^{-1}$. This value is remarkably close to our measurement of mean required vecuronium steady-state infusion rate for steady-state 50% twitch depression during halothane–nitrous oxide anesthesia (group

C) of 28.8 mg·kg^{-1}·hr^{-1}. This represents the first comparison of the simultaneous muscle relaxant pharmacokinetic and pharmacodynamic modelling technique's Cpss$_{50}$ and clearance calculations with direct clinical experimental measurement.

In summary, this study measured the vecuronium infusion doses necessary to achieve steady-state 50 and 90% twitch force depression and found that during halothane–nitrous oxide anesthesia, vecuronium infusion dose variability and absolute required amounts were less than during fentanyl–nitrous oxide anesthesia. Clinically, if utilizing a mean required vecuronium infusion rate as a starting point, use of halothane–nitrous oxide anesthesia should (by reducing the patient variability in required dose) make establishment of a steady-state level of twitch depression with a continuous infusion of vecuronium easier than with use of fentanyl–nitrous oxide anesthesia.

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Sign of Complete Sympathetic Blockade:

Sweat Test or Sympathogalvanic Response?

Honorio T. Benzon, MD, S. C. Cheng, PhD, Michael J. Avram, PhD, and Robert E. Molloy, MD

BENZON HT, CHENG SC, AVRAM MJ, MOLLOY RE. Sign of complete sympathetic blockade: sweat test or sympathogalvanic response? Anesth Analg 1985;64:415–9.

The sensitivity, specificity, and accuracy of the cobalt blue and ninhydrin sweat tests were compared with the sympathogalvanic response (SGR) in assessment of complete sympathetic blockade. Patients were randomly assigned to receive epidural administration of either preservative-free physiologic saline solution and 80 mg methylprednisolone (group I, control group, 9 patients) or 1.5% lidocaine with 80 mg methylprednisolone (group II, sympathetic blocked group, 10 patients). In group I, there was one false positive SGR (absence of SGR) before the block and there were four false positive SGRs after the block. In comparison, there were no false positive sweat tests (absence of sweating) before and after injection in group I. In group II, there were three false positive SGRs and no false positive sweat test before injection. After injection, one patient with an upper level of sensory blockade at T5 had persistent SGRs and positive sweat tests (false negative results). The study showed the sensitivity of the SGR and the sweat tests to be 90%. The specificity of the SGR was 56% compared to 100% for the sweat tests. The accuracy of the SGR was 74% compared to 95% for the sweat tests.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—sympathetic. MEASUREMENT TECHNIQUES—sympathetic activity. SYMPATHETIC NERVOUS SYSTEM—blockade.

The sympathetic nerve supply to the skin controls vascular tone and sweat production. Measurements of sympathetic blockade include increase in skin temperature, increase in pulse amplitude, abolition of the sympathogalvanic response (SGR), and inability to sweat. Increases in skin temperature measured by contact thermometry or infrared thermography and by an increase in pulse amplitude measured by plethysmography are the commonly used signs of sympathetic blockade (1–4). Although increases in skin temperature and pulse amplitude signify sympathetic blockade, they do not indicate complete sympathetic blockade unless accompanied by abolition of the SGR or absence of sweating because skin temperature and pulse amplitude may increase even with a partial sympathetic blockade. Abolition of sweating and abolition of the SGR are the standard tests of complete sympathetic blockade (5,6). The SGR, however, is difficult to reproduce and is characterized by marked variation of individual responses to the different stimuli (7). Although the starch-iodine sweat test is messy and cumbersome (5), newer sweat tests, such as the cobalt blue (5) and ninhydrin (8) tests are easier to perform. The purpose of this study was to compare the reliability of the latter two tests against the SGR in patients who had complete sympathetic blockade.

Methods

ASA physical status I patients with low back pain and lumbosacral radiculopathy who had lumbar epidural steroid injections as part of their treatment were randomly assigned to one of two groups. The control group (group I) was given 6–8 ml of physiologic saline solution without preservative, with 80 mg methylprednisolone. The sympathetic blocked group (group II) was given 27–30 ml 1.5% lidocaine with 80 mg methylprednisolone. Randomized assignment of patients to the two groups was accomplished with a random number table. None of the patients had had surgery and all were presumed to have pain secondary to herniated intervertebral discs. Six of the nine patients in group I and seven of the eleven patients

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Address correspondence to Dr. Benzon, Northwestern Memorial Hospital Passavant Pavilion, Room 360, 303 East Superior St., Chicago, IL 60611.

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in group II had documented herniated discs by CAT scan or myelogram. The remaining patients had not had a CAT scan or a myelogram, but had documented radiculopathies by electromyography (EMG). All patients were alert and none had a history of diabetes mellitus or peripheral vascular disease. Although the patients were taking minor analgesics at the time of the study, no patients were taking drugs known to affect the SGR, including narcotics, major tranquilizers, anticholinergics, epinephrine, digitalis, steroids, or hexamethonium (6,9–11). The study was not blinded because possible local anesthetic blockade from the saline (7,12) and incomplete or delayed blockade from the local anesthetic (13) had to be evaluated. The study was approved by the Human Subjects Committee of Northwestern University, and written informed consent was obtained from all patients.

The blocks were done in a quiet area with a constant temperature (23 ± 1°C). The SGRs were recorded according to published technique (6): the right arm and left arm leads of the electrocardiogram (ECG) were placed on the dorsum and sole of the foot while the other leads were placed on the contralateral leg; the ECG machine lead selector switch was turned to lead I. The following stimuli were used in every patient in a random order: pin prick at the upper (unblocked) extremity; loud noise; and deep breath. Permanent SGR recordings were obtained from the ECG machine and displayed on a strip recorder.

Our method of preparation of the cobalt blue and ninhydrin filter papers were modified from those previously described (5,8). For the cobalt blue filter paper, we used 0.5 M $CoCl_2$ in 70% ethanol instead of in distilled water. Heating the filter paper was not required in the present method because 70% ethanol dries rapidly. For the ninhydrin paper, we used 2% ninhydrin in 70% ethanol with 1 ml of 4 M acetate buffer (pH 5.6) per 100 ml of solution. We used 70% ethanol rather than acetone as described by Dhuner et al. (8) because acetone dries very rapidly, resulting in uneven application of the ninhydrin over the filter paper. The solutions (cobalt blue or ninhydrin) were applied evenly on a Whatman #1 filter paper at 2 ml/100 cm^2. The papers were dried at room temperature and stored in a desiccator.

The sweat tests were performed in the following manner: the subjects' toes were wiped dry and the cobalt blue and ninhydrin impregnated filter papers were taped on them. A transparent tape was used so the change in color of the cobalt blue paper secondary to sweating could be seen. Sweating on the cobalt blue paper resulted in a change of color from blue to pink (5). In the ninhydrin test (8), sweating appeared as distinct purple dots on the filter paper after the paper was heated for 1–2 min. Each purple dot corresponds to a functioning sweat gland. If sweating was absent, heat generated by a 150-W bulb held 15 cm from the foot being tested was applied to the foot for up to 10 min. The 10-min limit was used because prior experience showed patients either sweated spontaneously or did so within 3 min of heat application.

In both groups, the SGR and sweat tests were performed before the epidural injection and 15–30 min after the injection. If the patients still sweated and their SGRs persisted after the local anesthetic injection in group II, the tests were repeated 15–30 min later.

Lower extremity sympathetic blockade after the epidural injection of local anesthetic was assumed to be present when there was sensory anesthesia from T8 to S5. Sensory blockade was evaluated by pin prick before the epidural injection and 15 min after the injection. If the SGR and sweat tests were positive after the epidural local anesthetic injection, sensory blockade was again evaluated 15–30 min later, together with the SGR and sweat tests. Sympathetic blockade was assumed to be absent in the patients given normal saline. Patients who developed patchy or incomplete sensory blockade (13) from the local anesthetic and patients who developed sensory blockade (new areas of deficits) (7) from the physiologic saline solution were noted. The absence of sweating or of the SGR before epidural injection in both groups and the disappearance of either the SGR or sweating after the saline injection (group I patients) were considered false positive results. The persistence of the SGR or sweating after the epidural local anesthetic injection (group II patients) was considered a false negative result. The sensitivity, specificity, and accuracy of the SGR and the sweat tests in confirming complete sympathetic blockade were evaluated using the following definitions: sensitivity of a test indicates the capacity for making a correct diagnosis in confirmed positive cases (14); specificity is the capacity for correct diagnosis in confirmed negative cases (14); and accuracy is the efficiency or correctness of a test, the ability of a test to show positive results in positive cases and negative results in presumed negative cases (14,15).

Results

Nineteen patients were studied, nine in group I and ten in group II. Two of the nine patients in group I were women; the average age of the nine patients was 37 yr (range 23–57). All patients in group II were men, with an average age of 40 yr (range 22–56).

One of the nine patients given epidural saline (group

I) developed diminished sensation at the L4 dermatome. In group II patients, the upper level of sensory blockade ranged from T4 to T8 and extended to the S5 dermatome. Six of the ten patients had complete sensory anesthesia. Four patients had dermatomal levels of complete and incomplete sensory anesthesia, the areas of incomplete anesthesia being in the L5–S1 dermatome (bilateral) in one patient and in the S1 dermatomes (bilateral) in the other three.

In group I, one patient had a false positive (no response) SGR to deep breathing before the block (Table 1). After the epidural saline injection, four of the nine patients had false positive SGRs (positive SGR that became negative after the injection): three of the four patients had a false positive response to one of the three stimuli, one patient had a false positive repsonse to all three stimuli. In comparison, there was no false positive result for the two sweat tests before or after the epidural saline injection, i.e., all patients sweated. In group II, three patients had false positive SGRs before the block. Two of the three patients each had a false positive response to one stimulus, and one patient had false positive responses to two of the three stimuli used. There were no false positive results on the sweat tests before the injection. After the epidural injection of local anesthetic, the SGRs were abolished and the sweat tests became negative in nine of ten patients. In one patient, the cobalt blue and ninhydrin sweat tests remained mildly positive, and he had mild responses to all the three SGR stimuli. The cobalt blue paper showed mottled pink patches 2–3 mm in size while the ninhydrin paper showed sparse purple dots. His SGR showed a small response 20 min after the injection. The SGR response increased 45 and 60 min after the injection. His upper level of sensory blockade was T5; the L5–S1 dermatomes were less numb 15 min and the S1 dermatomes were less numb 30 minutes after the injection than were the other blocked dermatomes.

Three patients in group I who required a heat lamp to sweat before the injection also required heating after the injection. Heat was applied for 2–3 min before the epidural injection and 3–6 min after injection. The remaining six patients sweated spontaneously before and after the injection. Before the epidural injection, their sweat tests became positive within 3–5 min of filter paper application. After the injection, their sweat tests became positive within 4–5 min of application. In group II, four patients required heat for 2–5 min to sweat, six patients had spontaneous positive sweat tests within 3–5 min. After the injection, the heat lamp was applied for up to 10 min in all patients. The cobalt blue filter paper, which had become pink with sweating, returned to its original blue color within 3–6 min in group I patients and within 3–10 min in group II patients. On the other hand, the purple dots on the ninhydrin paper did not fade, providing a permanent record of the results of the test. In all patients, the two sweat tests consistently gave the same results, whether positive or negative.

Table 1. SGR Responses before and after Epidural Injection of Saline (Group I) and Local Anesthetic (Group II)

	Before injection → after injection SGR height (mm)		
Patient	Pin prick stimulus	Deep breath stimulus	Loud noise stimulus
Group I			
1	28 → 9	9 → 9	29 → 24
2	9 → 31	14 → 12	41 → 0
3	32 → 10	24 → 9	30 → 16
4	18 → 0	19 → 0	22 → 0
5	12 → 9	4 → 4	8 → 9
6	37 → 22	9 → 13	26 → 23
7	32 → 9	33 → 0	35 → 23
8	44 → 13	0 → 24	31 → 0
9	22 → 30	24 → 29	24 → 17
Group II			
1	28 → 0	21 → 0	23 → 0
2	17 → 0	12 → 0	10 → 0
3	28 → 0	0 → 0	16 → 0
4	18 → 20[a]	23 → 25[a]	11 → 6[a]
5	8 → 0	6 → 0	16 → 0
6	10 → 0	17 → 0	15 → 0
7	12 → 0	8 → 0	13 → 0
8	0 → 0	5 → 0	0 → 0
9	0 → 0	4 → 0	11 → 0
10	23 → 0	21 → 0	18 → 0

[a] Post-injection SGR height is the average of those measured at 20, 45, and 60 min after the injection in patient 4.

Evaluation of the SGR and of the two sweat tests as reliable signs of complete sympathetic blockade showed the sensitivity of both the SGR and the sweat tests to be 90%. The specificity of the SGR was 56% compared to 100% for the sweat tests. The accuracy of the SGR was 74% compared to 95% for the sweat tests.

Discussion

Patients may have only partial relief of pain associated with sympathetic imbalance after a diagnostic sympathetic block either because the sympathetic blockade is incomplete or because their pain is due to several causes (e.g., combined reflex sympathetic dystrophy and somatic sensory pain). To eliminate incomplete sympathetic blockade as a factor, a reliable sign of complete sympathetic blockade is necessary.

Proof of completeness of sympathetic denervation is also needed after chemical or surgical sympathectomy. Increases in skin temperature and pulse amplitude have been the most commonly used signs of successful sympathetic blockade (1–4,16). However, temperature and pulse amplitude increases cannot signify complete sympathetic blockade unless accompanied by abolition of the SGR or absence of sweating because temperature and pulse amplitude will increase even with a partial sympathetic block.

In studies where abolition of the SGR was used as sign of complete sympathetic blockade, the SGR had several shortcomings. These included marked variations in the responses of patients to the different stimuli used (7), difficulty in obtaining a satisfactory recording under clinical conditions (11), and rapid habituation to the stimuli used (11). A study that used pin prick as the stimulus to elicit the SGR abandoned the test because of inconsistent results (4). Our study showed that some patients fail to respond at all to one stimulus while responding to other stimuli. Patient 8 in group I, for example, had a marked SGR response to pin prick, a moderate response to loud noise, and no response to deep breathing. Some of the recommended stimuli also seem inappropriate to us; these include a flash of bright light or the slam of a door (17). These are probably why the SGR is not widely used (11). It is apparent that another standard test of complete sympathetic blockade is necessary.

Abolition of sweating is another sign of complete sympathetic blockade (5). The starch-iodine test in which the material is spread over the limb being tested (18) has not become popular because it is so awkward to use. Cousins et al. have described the cobalt blue sweat test as an alternative (19). In their discussion of sympathetic neural blockade, Löfström et al. (5) also mentioned the ninhydrin method (8). We decided to compare these two sweat tests with the SGR and to observe any advantage one sweat test may offer over the other. Unlike Löfström et al. who recommended the application of heat for 30 min, we found the application of heat for 2–6 min to be adequate, using the change in color of the cobalt blue paper as an end point.

In the present study, the control group was given 6–8 ml physiologic saline solution to dilute the methylprednisolone. Injecting undiluted methylprednisolone is not advisable because the polyethylene glycol present in the methylprednisolone preparation may cause arachnoiditis (20,21). Dilution of the methylprednisolone with normal saline or local anesthetic lowers the concentration of the polyethylene glycol to avoid such a complication should the injection be made intrathecally (22). We did not inject a volume of saline comparable to the volume (27–30 ml) of local anesthetic given to patients in group II because we tried to avoid any possible local anesthetic blockade from the saline (7,12).

Physiologic saline may have a local anesthetic effect. Benzon et al. noted signs of sympathetic blockade accompanied by a reduction of pain in two patients given stellate ganglion block with 10 ml of preservative-free physiologic saline solution (12). After an intrathecal injection of 5 ml or 10 ml of physiologic saline, Urban and McKain noted dermatomal hypesthesia, a diminution in SGRs, and a reduction of pain in 22 patients (7). They did not state whether the saline they used was preservative-free or contained 0.9% benzyl alcohol, a preservative with a local anesthetic effect (23). A subsequent study that used 5 ml of preservative-free physiologic saline concluded that intrathecal saline does not have a sympathetic blocking effect (4), although two of the ten patients had decreased responses to pin prick.

One of the four patients in group I whose SGR disappeared after saline injection (a false positive result) developed diminished sensation in the previously normal L4 dermatome. Although unable to cause demonstrable sensory blockade in other segments, the saline might have produced partial sympathetic blockade in the segments of the spinal cord that send sympathetic fibers to the lower extremities. The abolition of the SGR may reflect partial sympathetic blockade from the saline plus tolerance of the patient to the stimuli used to initiate the SGR; patients rapidly develop tolerance to the stimuli employed to elicit SGRs (11).

In group II, we decided on a minimum upper sensory level of blockade above T8 because previous studies documented reappearance of sympathetic activity in the lower extremities when the level of analgesia regressed to T8–T9 and below (24,25). Moore also recommends a level of at least the ninth thoracic dermatome (26). This level of blockade is needed because the preganglionic sympathetic fibers to the lower extremities originate from the T10 to L2 segments of the spinal cord (24). Our previous experiences with other patients with back pain showed that volumes of 25–30 ml of 1.5% lidocaine were required to produce a level of blockade above T8.

Delayed and incomplete ("feeling of less numbness") blockade can occur after epidural anesthesia, especially in patients with back pain (13). This phenomenon is not due to any interference of the local anesthetic effect by the steroid (13). We looked for incomplete blockade, especially at the T10–L2 segments, to explain any persistence of the SGR and unchanged sweat tests in the patients given local anesthetic. The four patients in Group II who had incomplete blockade at the L5 or S1 dermatome had herniated discs or radiculopathies in the same area. The delayed blockade in these dermatomes may have been due to inflammation or fibrosis of the nerve roots (13) or to the wider diameter of these nerve roots in comparison to other nerve roots (27). Three of the four patients had their SGRs and sweat tests abolished. The remaining patient had mildly positive SGRs and sweat tests. His upper level of sensory blockade was T5, but his S1 dermatomes were not as numb as the other dermatomes 30 min after the epidural injection. A possible explanation for the persistent sympathetic activity in this patient may be that epidural anesthesia causes sympathetic blockade mostly at the preganglionic level. It may also block some of the paravertebral sympathetic ganglia after some of the local anesthetic has exited through the intervertebral foramina. If very few of the paravertebral ganglia are blocked, unblocked sympathetic fibers above the level of anesthesia may conduct impulses to the postganglionic fibers terminating in the lower extremity through the paravertebral sympathetic chain. The numerous connections between sympathetic preganglionic and postganglionic neurons facilitate transmission of these impulses (24).

Our study showed that the two sweat tests are more accurate and specific tests of complete sympathetic blockade than the SGR. Either sweat test is acceptable. However, we recommend simultaneous use of the two tests because they complement each other. The observed change in color of the cobalt blue when sweating is present prevents unnecessary prolonged application of heat with consequent burning of patients' skin, and the ninhydrin test is suitable as a permanent record.

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Malignant Hyperthermia:

Is Etomidate Safe?

Maya S. Suresh, MD, and Thomas E. Nelson, PhD

SURESH MS, NELSON TE. Malignant hyperthermia: is etomidate safe? Anesth Analg 1985;64:420–4.

The safety of etomidate for induction of anesthesia in malignant hyperthermia-susceptible (MHS) pigs was evaluated in a two-phase experiment. Two litters of Purebred Poland China pigs, one MHS (n = 4) and the other malignant hyperthermia-resistant (MHR)(n = 4) were used. Phase I compared MHS vs MHR animals in terms of cardiovascular, metabolic, and skeletal muscle rigidity responses to etomidate and fentanyl anesthesia and to a subsequent malignant hyperthermia (MH) challenge with halothane–succinylcholine. When three of the four criteria for the diagnosis of MH occurred (rigidity, tachycardia, or increases in temperature or end-tidal CO_2*) in an animal, phase I was terminated. In phase II, only the MHS animals were used and experimental procedures were as in phase I except thiopental replaced etomidate. In phase I, evidence was inadequate to support the diagnosis of MH based upon responses of MHS pigs to the infusion of etomidate even though the infusion of etomidate in MHS pigs was associated with statistically significant increases in body temperature and plasma lactate levels above those observed in MHR pigs. Heart rate and bicarbonate levels were lower in MHS than in MHR pigs during etomidate infusion. With discontinuation of etomidate and a subsequent challenge with halothane–succinylcholine, all four pigs developed the MH syndrome within 15–30 min. Thiopental replacement of etomidate in the phase II experiment resulted in a twofold greater time (45–75 min) for halothane–succinylcholine to trigger MH in the susceptible pigs. We conclude that etomidate does not trigger MH in MHS pigs, but compared to thiopental, it predisposes the MHS pigs to a more rapid onset of the MH syndrome triggered by halothane–succinylcholine.*

Key Words: ANESTHESIA, INTRAVENOUS. HYPERTHERMIA—malignant.

Malignant hyperthermia (MH) is a catastrophic, hypermetabolic syndrome induced by commonly used general anesthetics (1). The anesthetic agents that can be used safely in known MH-susceptible (MHS) patients are few (1). Etomidate, a nonbarbiturate intravenous hypnotic agent, has certain advantages when compared to thiopental. Etomidate maintains cardiovascular stability and does not cause marked respiratory depression or histamine release (2,3). However, etomidate is associated with myoclonic movements during induction of anesthesia in as many as 70% of patients (4). It is not known whether this side effect or other effects of etomidate can produce the MH syndrome in MH-susceptible patients. The present study was undertaken to evaluate the safety of etomidate as an induction agent in MH-susceptible pigs.

Methods

Four littermate, purebred Poland China pigs, the offspring of MHS parents and biopsy proven for MHS, were used in this study. In vitro muscle contracture responses to caffeine, halothane, or both disclosed a phenotype H (5,6) for each. Four other purebred Poland China pigs, unrelated to the MHS litter and proven by muscle contracture tests not to be MHS were used as controls (MH-resistant, MHR). The average weights for MH and control pigs were 38 ± 6.8 and 38.7 ± 1.3 kg, respectively. Both litters were used in experimental phase I, which compared the responses to etomidate and to a subsequent halothane–succinylcholine challenge.

Phase I

In this phase I experiment, each pig was premedicated intravenously with diazepam (0.05 mg/kg) and fentanyl (2 μg/kg). Anesthesia was then induced by the

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Address correspondence to Dr. Suresh, Department of Anesthesiology E-91, University of Texas Medical Branch, Galveston, TX 77550-2778.

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intravenous administration of additional fentanyl (5 μg/kg) followed by etomidate (0.9 mg/kg). Orotracheal intubation immediately followed, after which respirations were manually assisted to maintain an end-tidal CO_2 of approximately 5% while breathing 70% N_2O–30% O_2. Anesthesia was maintained with continuous infusion of etomidate at the rate of 0.08 $mg \cdot kg^{-1} \cdot min^{-1}$, and incremental doses of fentanyl, 1 μg/kg every 30 min in addition to 70% nitrous oxide. The effective doses of etomidate used in the present study were determined in preliminary studies utilizing other pigs. These doses of etomidate were, when used in conjunction with other agents, adequate for induction and maintenance of anesthesia. A peripheral arterial cutdown was performed, a 3F catheter was inserted, and arterial pressure was continuously monitored and recorded. Rectal temperature, heart rate, electrocardiogram, and end-tidal CO_2 were continuously monitored and recorded at 15-min intervals throughout each experiment. Arterial blood was obtained at 15-min intervals for the measurement of blood–gas tensions, pH, and lactate. Lactate was determined enzymatically by a spectrophotometric technique.

After a total of 5 mg/kg of etomidate had been administered, the infusion was stopped, the nitrous oxide was discontinued, and the MH challenge initiated by ventilating the animals with 2% halothane in oxygen for 1 hr followed by succinylcholine (2 mg/kg intravenously) every 15 min while halothane was continued for an additional hour. When three of four criteria for MH were present (i.e., rigidity, tachycardia, or increases in end-tidal CO_2 or temperature), MH was diagnosed and the experiment concluded. Each animal developing these MH clinical criteria was treated with dantrolene (2.5 mg/kg) and each had an uneventful recovery.

Phase II

Phase II of the experiment involved only the MHS pigs that were used 10 days after the phase I experiment. Experimental procedures in phase II duplicated those in phase I except that thiopental replaced etomidate in the following manner. The dose of thiopental used for induction of anesthesia was 20 mg/kg and maintenance of anesthesia was with thiopental (2.5 mg/kg) every 5 min for the time period equal to that over which etomidate was infused in the same animal. The halothane–succinylcholine challenge followed as in phase I. The MHS animals gained, on the average, 2 kg between phase I and II experiments.

Data were statistically analyzed by paired *t*-test and by analysis of variance. Because phase I consisted of both MHS and MHR pigs, the investigators were blinded to the MH-susceptibility of each animal.

Results

Phase I

Immediately after induction of anesthesia with fentanyl and etomidate, myoclonic movements occurred in 50% of the animals with no differences observed in the incidence or severity of these movements in MHS and MHR pigs. During maintenance of anesthesia with etomidate infusion, slight to moderate tremors occurred intermittently in all animals. However, the level of anesthesia was adequate for surgical cutdown for arterial cannulation. Variables measured in MHS and MHR animals during phase I are presented in Tables 1 and 2. No statistically significant changes in these variables occurred within either group of pigs during the time course of the etomidate infusion. Comparing variables between the two groups of pigs during etomidate infusion showed that heart rate and bicarbonate levels were significantly lower ($P < 0.05$), while lactate levels and temperature were significantly higher in MHS pigs. Based on the four MH diagnostic criteria, MH was not observed in any animal during the etomidate infusion period.

Within 15 min of initiation of halothane–MH challenge, three of the four MHS pigs developed three of the four criteria of MH. The fourth MHS pig developed these symptoms 30 min after onset of halothane anesthesia. None of the MHR pigs developed any of the criteria suggestive of MH. After the development of MH diagnostic criteria, each MH episode was immediately treated by intravenous administration of dantrolene (2.5 mg/kg).

Phase II

The thiopental-treated MHS pigs developed, after exposure to halothane, the criteria for an MH crisis similar to those produced when treated with etomidate (Figs. 1–3). However, time to development of these criteria was significantly ($P < 0.005$) longer in the thiopental-treated than in the etomidate-treated pigs (58 ± 10 and 18 ± 6 min, respectively) (Table 3). Prior to the administration of halothane in phase II, the thiopental-treated animals had lower lactate levels and lower body temperature than they did when treated with etomidate (Figs. 1,2). Although onset of MH symptoms was delayed by thiopental, when compared to etomidate, the rate of development and extent of metabolic acidosis, increases in temperature, and skeletal muscle rigidity were similar to those observed when the animals were treated with etomidate (Figs. 1–3). It appears from Figure 2 that the increases in temperature in MHS pigs in phase II is inconsequential; however, each individual MHS animal had an increase in body temperature, but these occurred

Table 1. Heart Rate, Mean Arterial Pressure (MAP), End-Tidal CO_2, and Rectal Temperature during Etomidate Infusion Followed by a Halothane–Succinylcholine Challenge in MHS and MHR Pigs

Variable	Group	Etomidate					2% Halothane				Halothane–succinylcholine			
Time (min)		15	30	45	60	75	90	105	120	135	150	165	180	195
Heart rate	MHR[a]		79	83	82	76	108	128	125	106	98[b]	112	107	130
(beats/min)	MHS		65	61	69	61	69	174	131	94				
MAP	MHR		121	127	130	134	127	121	93	81	88	99	92	97
(mm Hg)	MHS		105	146	132	128	137	110	101	123				
End-tidal CO_2	MHR	5.6	4.8	4.7	4.8	4.6	4.7	4.3	4.7	4.6	4.9	4.6	4.8	4.4
(vol %)	MHS	4.9	4.3	5.1	4.9	4.9	4.8	7.6	6.9	4.8				
Temperature	MHR	37.9	37.6	37.6	37.6	37.6	37.6	37.4	37.3	37.2	37.1	36.9	36.7	36.6
(°C)	MHS	38.2	38.3	38.3	39.2	38.3	38.4	38.4	38.6	38.7				

[a] MHR: $n = 4$, MHS: $n = 4$.

[b] During halothane challenge MH was triggered in three MHS pigs at 105 min; in the fourth pig, MH was triggered at 120 min. After MH was triggered, halothane was discontinued, dantrolene treatment initiated, and the experiment terminated.

Table 2. Arterial pH, Pa_{CO_2}, Pa_{O_2}, HCO_3^-, and Lactate during Etomidate Infusion Followed by Halothane–Succinylcholine Challenge in MHS and MHR Pigs

Variable	Group	Etomidate				2% Halothane				Halothane–succinylcholine			
Time (min)		30	45	60	75	90	105	120	135	150	165	180	195
pH	MHR[a]	7.39	7.47	7.45	7.41	7.42	7.45	7.44	7.42	7.45[b]	7.41	7.37	7.43
	MHS	7.41	7.39	7.41	7.43	7.38	7.25	7.18	7.24				
Pa_{CO_2}	MHR	39	33	36	38	38	35	35	36	33	36	37	37
(torr)	MHS	34	37	34	36	38	48	35	35				
Pa_{O_2}	MHR	184	201	194	187	296	407	397	401	407	402	418	359
(torr)	MHS	212	203	256	254	201	380	434	431				
HCO_3^-	MHR	22	23	24	22	24	24	23	23	22	22	23	24
(mEq/L)	MHS	20	22	20	22	22	20	16	15				
Lactate	MHR	2.3	2.0	1.8	1.9	1.8	1.6	2.0	2.3	2.6	2.8	2.8	2.6
(mm/L)	MHS	2.9	3.0	3.2	3.3	3.4	5.5	12.1	14.2				

[a] MHR: $n = 4$, MHS: $n = 4$.

[b] During halothane challenge, MH was triggered in three MHS pigs at 105 min; in the fourth pig, MH was triggered at 120 min. After MH was triggered, halothane was discontinued, dantrolene treatment initiated, and the experiment terminated.

at different intervals during halothane challenge. Therefore, this apparent discrepancy is due to the fact that animal temperatures were averaged across time.

Discussion

There are few anesthetics considered safe for use in the MHS subjects (1). It is important, therefore, to determine the efficacy and safety of any new anesthetic agent, such as etomidate, in patients susceptible to MH.

The technique of etomidate administration in the present study, along with fentanyl and nitrous oxide, provided adequate anesthesia and satisfactory surgical conditions, in both MHS and MHR pigs. The principal side effect attributable to etomidate was a 50% incidence of mild myoclonic movements observed in both groups of pigs. Myoclonic movements reappeared on emergence or during light phases of anesthesia, the latter being readily reversed by scheduled doses of fentanyl.

Certain significant findings of this study are apparent. First, during the period of etomidate infusion into the MHS pigs and prior to the MH challenge, clinical evidence was insufficient to establish the diagnosis of MH, based on the fact that there was no tachycardia, rigidity, or increase in the end-tidal CO_2. The second significant finding in this study was that although the experimental criteria for the diagnosis of MH were not met, there were significant differences in cardiovascular and biochemical findings between the MHS and MHR pigs during the etomidate infusion period in phase I. Compared to the MHR pigs, heart rate and bicarbonate levels were lower; body temperature and arterial lactate levels were higher in MHS pigs. The higher body temperature and lactate levels in MHS animals probably reflect an increased muscle activity that is produced by etomidate. However, our clinical observations based on the degree and incidence of muscle tremors during etomidate infusion did not detect any differences between the MHS and MHR pigs. In view of available data we

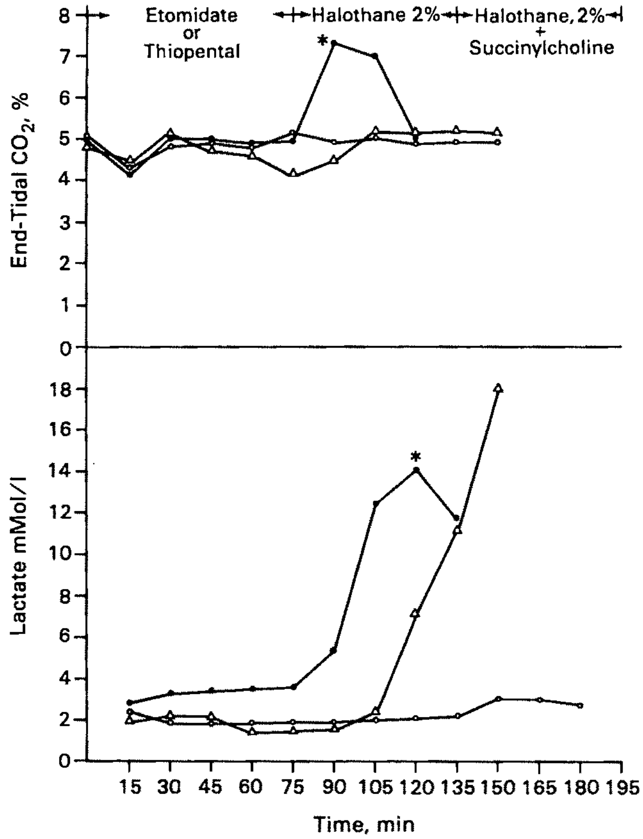

Figure 1. End-tidal carbon dioxide and blood lactate levels in MHR and MHS pigs during etomidate or thiopental treatment followed by halothane and halothane-plus-succinylcholine challenge. MHS–etomidate (●——●); MHS–thiopental (△——△); MHR-etomidate (○——○). (*After MH trigger, halothane was discontinued, dantrolene treatment initiated, and experiment terminated.)

cannot discriminate between two possible mechanisms for the observed increases in temperature and lactate levels. It may be that etomidate activates MHS muscle more than MHR muscle, but we were not able to differentiate this clinically. Such differentiation requires more discriminating methods to quantitate muscle activation. Alternatively, it is possible that the same degree of muscle activation produced more heat and lactate in the MHS pig muscle in the presence of etomidate.

The third significant finding in this study was the difference in responses of MHS pigs in phase I (etomidate) vs phase II (thiopental). Compared to the etomidate-treated MHS pigs, the same pigs receiving thiopental required a twofold longer time of halothane administration before the criteria for an MH diagnosis were met. The administration of thiopental delays the onset of MH in MHS pigs as shown by other investigators (7). Prior to halothane challenge, pigs receiving thiopental had lower body temperature and lower arterial lactate levels than did the same animals receiving etomidate. One possibility is that thiopental

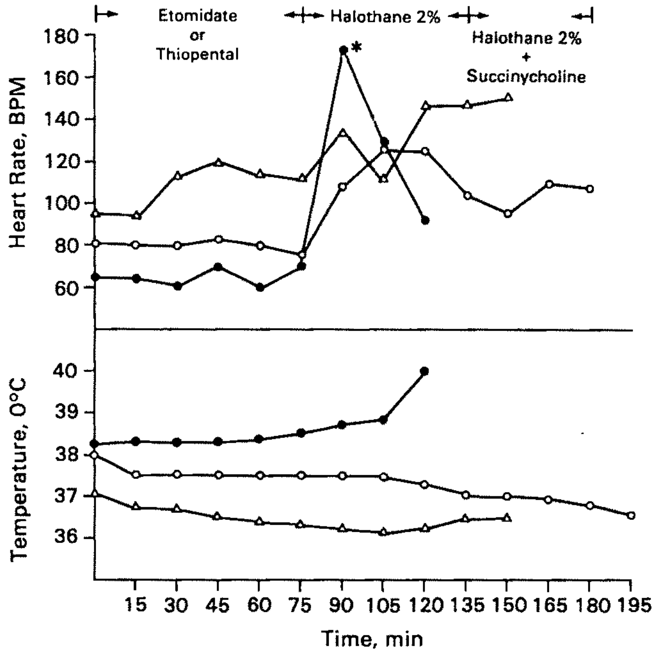

Figure 2. Heart rate and body temperature in MHR and MHS pigs during etomidate or thiopental treatment followed by halothane and halothane-plus-succinylcholine challenge. MHS–etomidate (●——●); MHS-thiopental (△——△); MHR–etomidate (○——○). (*After MH trigger, halothane was discontinued, dantrolene treatment initiated, and experiment terminated.)

Figure 3. Serum HCO_3 and pH levels in MHR and MHS pigs during etomidate or thiopental treatment followed by halothane and halothane-plus-succinylcholine challenge. MHS–etomidate (●——●); MHS–thiopental (△——△); MHR–etomidate (○——○). (*After MH trigger, halothane was discontinued, dantrolene treatment initiated, and experiment terminated.)

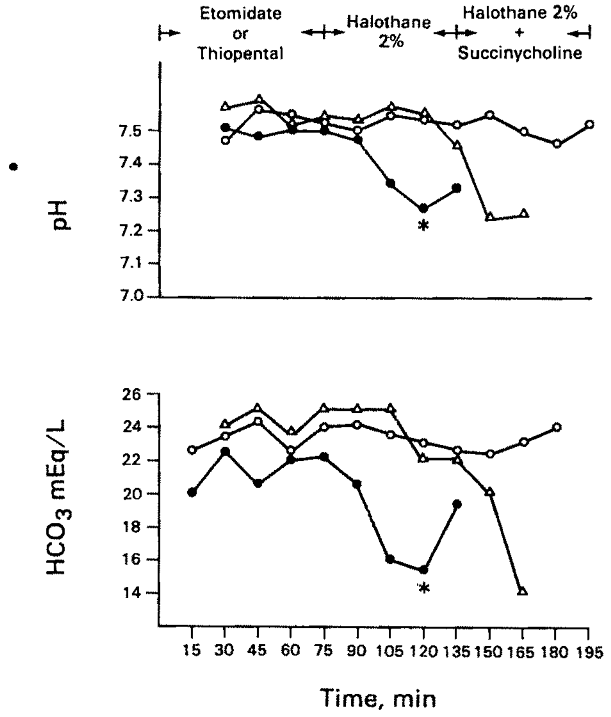

Table 3. Comparison of Time Required to Trigger MH in MHS Pigs from the Start of Halothane in Phases I and II

	Phase I[a]	Phase II[a]
MHS pig	Time (min)	Time (min)
1	15	55
2	30	60
3	15	45
4	15	75

[a] Phase I is etomidate pretreatment and Phase II is thiopental pretreatment (see text for details).

decreases metabolic rate and increases heat loss by vasodilation and, by so doing, protects against triggering MH. In contrast, etomidate may increase muscle activity and thus increase metabolic rate and body temperature.

Based on the experimental criteria and results of this study, it can be concluded that etomidate alone does not trigger the MH syndrome in the MHS pigs. Compared with thiopental, etomidate protects the MHS animal less than thiopental. It is not yet known whether these results can be extrapolated to humans, but if so, then thiopental has a greater margin of safety than etomidate in MH-susceptible humans.

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A Comprehensive Computer System for Anesthetic Record Retrieval

G. Bashein, MD, PhD, and C. R. Barna, BA

BASHEIN G, BARNA CR. A comprehensive computer system for anesthetic record retrieval. Anesth Analg 1985;64:425–31.

We have developed computer software to store data on all surgical and obstetrical anesthetics administered by our department. The computer system provides information for monitoring the residency training program, department and operating room management, professional fee billing, and research. It imposes little additional workload on our clinical personnel, who use simple codes to record the necessary data directly on the anesthetic record. Department secretarial staff transcribe data from both the anesthesia and operating room records into the computer file, which is then available for producing scheduled reports and for answering inquiries from a video terminal. The system employs extensive manual and computer verification to minimize errors and omissions in the data. We report design details and more than 3.5 years experience with this system, which is now used at four affiliated teaching hospitals, has over 50,000 cases on file, and adds more than 1800 cases monthly.

Key Words: RECORDS, ANESTHESIA—computerized. STATISTICS.

During surgery, an important part of the anesthetist's task is to document information about the patient, the operation, and the anesthetic for the written medical record. Before the advent of automatic data processing equipment, this information was not readily retrievable, but now computers make it potentially accessible for use in education, research, operating room management, and billing.

Although suitable computers have been available widely in hospitals for over a decade, few data bases of anesthetics have been reported, and only two reports (1,2) contain sufficient detail to aid prospective designers. The reported systems are divided among those used by anesthesia departments (1–4), nursing administration (5), and hospital data processing organizations (6,7). Ideally, any surgical information system should serve the needs of all users and contain information abstracted from both the anesthesia record and the operating room record. Rovenstine (8) used a punched card system in 1934 to relate the information in these two documents and discussed its value for improving patient care, yet none of the recently reported systems appear to function similarly.

Our department had two previous computerized systems for surgical data collection, spanning some 12 years, but these systems suffered from major shortcomings that limited their usefulness and finally led to their discontinuation. We profited from those earlier experiences when we designed the current data base, which has now been used successfully for over 3.5 years. Because the system has a number of novel features not described previously, we report the design details and our experience with it.

Planning the System

Our initial task was to select the data elements to be stored. Although our charge was to monitor resident training activities, we also sought to design a comprehensive system to meet other anticipated needs without redundant data entry. Our department's previous experience showed that the quality of data provided by personnel in the operating room deteriorates rapidly as the requested quantity increases, so we planned to ask for only the minimum amount necessary to meet the anticipated needs. We carefully reviewed our departmental requirements, those of our professional fee billing organization, the operating room, and the American Board of Anesthesiology (for reporting training activity), arriving at the list of essential items shown in Table 1. We deliberately omitted intraanesthetic complications, because without an independent reporter the inevitable underreporting would lead to falsely favorable statistics.

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Address correspondence to Dr. Bashein, Department of Anesthesiology, RN-10, University of Washington, Seattle, WA 98195.

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Table 1. Data Elements from Anesthesia Record

Element name	Length (characters)
Hospital number[a]	9
Patient last name[a]	16
Patient first initial[a]	1
Patient middle initial	1
Date of birth[a]	8
Anesthetic agent/technique #1[a]	3
Anesthetic agent/technique #2 and #3	6
ASA physical status[a]	2
Sex[a]	1
ICDA diagnosis code[a]	7
Department study code	5
Faculty study code	5
Resident or CRNA identification[a]	4
Attending staff identification[a]	4
Date of operation[a]	8
Anesthesia starting time[a]	4
Anesthesia ready time	4
Surgery starting time	4
Surgery ending time	4
Anesthesia ending time[a]	4
First CPT code[a]	5
Second and third CPT codes	10
Nonstandard relative value	2
Professional fee discount	1
Monitors and qualifying circumstances (6)	6
Anesthetizing location[a]	2

[a]Denotes required items.

The next decision concerned how best to acquire these data and how to enter them into the computer. Possible sources included the anesthesia record, the operating room record, or coding forms prepared solely for this purpose. Possible data entry modes included key entry at a video display terminal, either by the clinical personnel themselves or by secretarial personnel, and automatic entry using mark-sense forms (similar to those used on standardized examinations) and an optical reader. Our previous system had used mark-sense forms covering both sides of a standard-size sheet of paper. The forms required too much effort to complete, they frequently became lost, and monthly batch processing did not allow for discovery of errors and omissions in time to correct them easily. Therefore, we chose key entry directly from the office copy of the anesthesia record, avoiding the additional labor and source of error from a separate form. We also expected our personnel to be more careful about writing on the official medical record than they had been on the auxiliary form. The anesthesia record was redesigned for this purpose, with the items necessary for computer entry written in their traditional places, but in color-shaded boxes for emphasis and using simple mnemonic codes where possible (see Fig. 1).

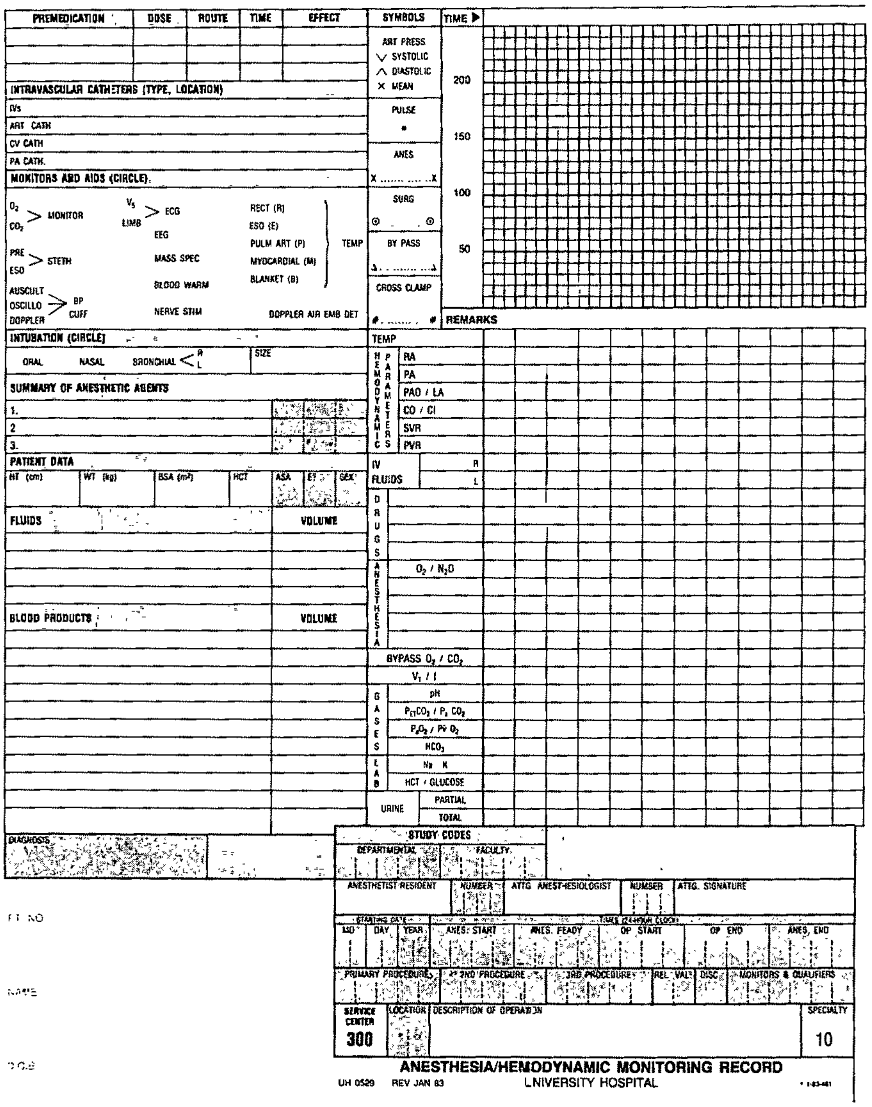
We rejected the possibility of direct keyboard entry by the clinical personnel because it has been shown to be unworkable in other medical settings. Instead, we planned to have the secretaries in each hospital use computer terminals and enter the data promptly on the first business day after the operation. Thus errors and omissions would be discovered and the forms returned for correction while the events were still fresh in the minds of the clinical personnel. To minimize errors, we planned to have the computer verify the entered data interactively and produce a log of the cases for manual reconciliation with the operating room log.

When our department's earlier data bases were designed, general purpose data base management software was not available to facilitate data storage and manipulation. Although the computer was programmed in Fortran to accept input, to write the data on magnetic tape, and to generate routine reports, there was no capability to produce ad hoc reports or to answer questions not anticipated when the programs were written. Since then, versatile data base management software (System-1022, Software House, Cambridge, MA) became available for the mainframe computer (DECsystem-10, Digital Equipment Corporation, Maynard, MA) in our Health Sciences Center, and we chose to use this rather than a dedicated microcomputer for several reasons. First, we expected that the programming would be easier with this data management software and a flexible screen-formatting data entry package developed locally. Second, the expected processing and disk storage requirements would tax the available microcomputer systems. Third, our computing center provides for simultaneous telephone-line access from remote hospitals, and finally, it has an elaborate disk file protection arrangement and daily magnetic tape backup of the disk to ensure the confidentiality, security, and safety of our data.

System Design

Coding and Data Entry

The coding of anesthetics is problematic. No widely accepted scheme is available, and it is difficult to describe succinctly the various combinations of anesthetic techniques and drugs. We decided that the essential descriptors of a general anesthetic are the maintenance agents used, so we do not tabulate the induction agents, muscle relaxants, or other adjuvant drugs. For regional anesthesia, we decided that the essential element is the technique employed, and we omit entering the local anesthetic agent(s). When balanced general anesthesia or combined regional–general anesthesia is administered, it is often difficult to state which is the primary and which are the aux-



PREMEDICATION	DOSE	ROUTE	TIME	EFFECT

INTRAVASCULAR CATHETERS (TYPE, LOCATION)

IVs

ART CATH

CV CATH

PA CATH.

MONITORS AND AIDS (CIRCLE)

O_2 / CO_2 > MONITOR
V_5 / LIMB > ECG
EEG
MASS SPEC
BLOOD WARM
NERVE STIM
PRE / ESO > STETH
AUSCULT / OSCILLO / DOPPLER > BP CUFF
RECT (R) / ESO (E) / PULM ART (P) / MYOCARDIAL (M) / BLANKET (B) } TEMP
DOPPLER AIR EMB DET

INTUBATION (CIRCLE)

ORAL NASAL BRONCHIAL < R / L
SIZE

SUMMARY OF ANESTHETIC AGENTS

1.
2
3.

PATIENT DATA

HT (cm)	WT (kg)	BSA (m²)	HCT	ASA	E?	SEX

FLUIDS	VOLUME

BLOOD PRODUCTS	VOLUME

SYMBOLS
ART PRESS
∨ SYSTOLIC
∧ DIASTOLIC
× MEAN
PULSE
●
ANES
X X
SURG
⊙ .... ⊙
BY PASS
Δ .... Δ
CROSS CLAMP
....

TIME ▶
200
150
100
50

REMARKS

TEMP
HEMODYNAMIC PARAMETERS: RA / PA / PAO / LA / CO / CI / SVR / PVR
IV FLUIDS: R / L
DRUGS
ANESTHESIA: O_2 / N_2O
BYPASS O_2 / CO_2
V_T / f
GASES: pH / $P_{ET}CO_2$ / P_aCO_2 / P_aO_2 / $P\bar{v}O_2$ / HCO_3
LAB: Na K / HCT / GLUCOSE
URINE: PARTIAL / TOTAL

DIAGNOSIS

STUDY CODES
DEPARTMENTAL | FACULTY

ANESTHETIST/RESIDENT | NUMBER | ATTG. ANESTHESIOLOGIST | NUMBER | ATTG. SIGNATURE

STARTING DATE: MO | DAY | YEAR
TIMES (24-HOUR CLOCK): ANES. START | ANES. READY | OP START | OP END | ANES. END

PRIMARY PROCEDURE | 2ND PROCEDURE | 3RD PROCEDURE | REL. VAL. | DISC. | MONITORS & QUALIFIERS

SERVICE CENTER 300 | LOCATION | DESCRIPTION OF OPERATION | SPECIALTY 10

PT NO

NAME

DOB

ANESTHESIA/HEMODYNAMIC MONITORING RECORD
UH 0520 REV JAN 83 UNIVERSITY HOSPITAL 1-83-461

Figure 1. Combined anesthetic record–data entry form.

iliary anesthetics, so we allow entry of up to three for each operation without implying any order of precedence. The three-letter mnemonic codes for general and regional anesthetics are shown in Table 2. To record use of invasive monitors and other unusual situations, we devised the single-letter codes shown in Table 3 and allow recording of up to six of them, in any order, in the lower right corner of the anesthetic record.

For the remaining data, we use standardized encoding methods to the extent possible. The anesthetist encodes the operations (up to three per anesthetic) while in the operating room, using the five-digit CPT-4 system (9). We think that the coding should be performed when the surgeon is available for confirmation, because often there are distinct codes for operations that differ only slightly from the anesthetic viewpoint, but differ importantly so far as chart review or operating time statistics are concerned. We do have the patient's diagnosis encoded postoperatively by our secretaries (10); it is used only for billing purposes and need not be precise because similar information is available from our medical records department computer. Personnel are identified by standard four-digit codes assigned by the School of Medicine, and patient physical status is described by the familiar American Society of Anesthesiologists code.

We also made provision for special study codes, allowing staff members to readily identify a particular series of patients or to link our data base to another one for research purposes. A total of ten alphanumeric characters is allowed for these codes, five with universal, department-wide definition, and five defined by individual faculty members for their own

Table 2. Anesthetic Agents and Techniques

Code	Agent/technique
1. General anesthetic agents	
BAR	Barbiturate
ENF	Enflurane
HAL	Halothane
ISF	Isoflurane
KET	Ketamine
MOF	Methoxyflurane
N2O	Nitrous oxide
NAR	Narcotic
XGA	Other general anesthetic
2. Regional anesthetic techniques	
A. Subarachnoid block	
SAB	Subarachnoid block
B. Epidural blocks	
CAU	Caudal block
CEP	Cervical epidural block
LEP	Lumbar epidural block
TEP	Thoracic epidural block
C. Nerve root blocks	
CPB	Cervical plexus block
CPV	Cervical paravertebral block
ICB	Intercostal block
LPV	Lumbar paravertebral block
TPV	Thoracic paravertebral block
TSB	Transsacral block
D. Visceral nerve blocks	
CEL	Celiac plexus block
LSB	Lumbar sympathetic block
SGB	Stellate ganglion block
E. Cranial nerve block	
CNB	Cranial nerve block (any)
F. Upper extremity blocks	
AXB	Axillary block
ISB	Interscalene block
IVU	IV regional, upper extremity
SCB	Supraclavicular block
XUE	Other upper extremity block
G. Lower extremity blocks	
4NB	4-nerve block (lower extremity)
FEM	Femoral nerve block
IVL	IV regional, lower extremity
PCB	Psoas compartment block
SCI	Sciatic nerve block
SFB	Sciatic/femoral block
XLE	Other lower extremity block
H. Catheter reinjection	
INJ	Reinjection epidural cath
I. Miscellaneous block	
XRA	Other regional anesthetic
3. Monitoring	
MON	Monitor only

Table 3. Monitors and Qualifying Circumstances

Code	Definition
A	Arterial cannulation
C	Central venous cannulation
E	Electroencephalographic monitoring
H	Use of controlled hypotension
I	Intracranial pressure monitoring
M	Mass spectrometer monitoring
S	Pulmonary artery cannulation
T	Use of hypothermia
U	Upright (sitting) position
X	Use of extracorporeal circulation

purposes. Although used infrequently, this feature has been invaluable on a few occasions.

Although our original intent was to design the simplest possible system, after two years of operation we found that a few additions would greatly add to its overall utility. By including identification of the surgeon(s) and entering operations done under local anesthesia without anesthetist standby, we enhanced the system's usefulness for operating room management, because we can accumulate time statistics by surgeon and analyze overall operating room utilization. The surgical departments have expressed interest in using our data, and including some additional information makes sharing data (and computer charges) more attractive to them. To accommodate these additions to the system, we added shaded boxes to the operative record (prepared by the circulating nurse) and incorporated the additional information (shown in Table 4) into the data base. The third copy of the modified operative record has an adhesive strip, and at the end of the operation it is attached back-to-back to the anesthetic record and its data are entered into the computer at the same time. This feature has been implemented at University Hospital and is now being added at the other hospitals.

For data entry, the screen of the video display terminal is formatted to duplicate portions of the anesthetic and operative records. The computer checks the data interactively for duplication, completeness, and internal consistency; it also asks for verification of improbable values (see Table 5). The data entered for any given anesthetic may vary from 15 elements (78 characters) to 33 elements (totaling 126 characters), and the resulting computer storage requirement, including the computer-generated indices to aid retrieval, is approximately 56 (36-bit) words (equivalent to approximately 282 bytes). In addition to the main disk file of anesthetics, we need separate files for verification of CPT codes, personnel identification codes, anesthetic codes, monitoring codes, anesthetizing location codes, and departmental special study codes.

Reports

Software was written to generate the following reports:[1]

Daily log. A daily log of anesthetics for each hospital.

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[1] Samples and descriptions of these are available from the authors on request.

Table 4. Data Elements from Operative Record

Element name	Length (characters)
Attending surgeon	4
Resident surgeons (2)	8
Consultant surgeon	4
Attending surgeon present/scrubbed status	1
Inpatient/outpatient status	1
Wound classification (clean, dirty, etc.)	1

Weekly professional fee billing. The individual patient charges are forwarded to our billing organization on magnetic tape.

Monthly reports summarizing hospital activity. Activity is broken down by numbers of cases and anesthesia time, overall and for specialized services, such as open-heart, neurosurgery, and obstetrics. Comparison of monthly and fiscal year-to-date activity and professional fee billing is made for estimating future income and personnel requirements. The types of anesthesia and use of invasive monitoring are tallied as an aid to overseeing the training activities. The monthly summary statistics are also accumulated in a disk file for generating graphs or long-term trend reports on clinical activity.

Monthly individual activity reports for each department member. These are issued promptly at the completion of the month and contain statistical summaries and, optionally, a detailed listing of individual cases. In addition, an annual summary of each resident's activity is prepared for the American Board of Anesthesiology.

Interactions between individual residents and faculty members (by number of cases and number of hours of anesthesia). This report is compiled at the end of each resident rotation to determine which staff and residents are asked to evaluate each other's performance. It helps to reduce the number of evaluations requested, and assures that the evaluations are based upon a significant amount of interaction.

Workload analysis. Reports have been developed that break down activity during regular and nonregular hours for each hospital and for specialty services. These take into account the starting and ending times of the regular workday, call time changeover on weekends and holidays, the dates of official university holidays, and they also properly apportion the time of cases that overlap regular and nonregular hours. These reports have been extremely useful in making decisions regarding staffing requirements, remuneration for call activity, and time-off allocation.

Table 5. Checking Performed on Data Entry

1. Operation date not greater than today's date.
2. Hospital number check digit valid.
3. No duplication of anesthetic agent/techniques.
4. No duplication of procedure codes.
5. No duplication of monitor/qualifier codes.
6. Patient sex appropriate to operative procedure.
7. Starting/ready/ending times consistent.
8. Diagnosis code in correct form.
9. Verify that codes for procedures, anesthetics, monitors, location, and personnel identification are found in their respective files of valid codes.
10. Operator must confirm operation duration more than 12 hr, interval from anesthesia start to anesthesia ready more than 1 hr, patient age less than 15 days, operation date more than 15 days ago.
11. No duplication of already existing record.

Ad hoc reports. Interactive inquiry from a computer terminal has been useful in answering a variety of questions relating to departmental or operating room management, determining the patient population available for various clinical studies, and evaluating the training experience in regional anesthesia and in specialized kinds of surgery. The system also provides assistance for manual chart review by helping to identify the study population by age, sex, operative procedure, or other factors.

Results

Setting up the system required approximately three man-months of effort by a systems analyst and a faculty anesthesiologist. Because the system brought significant changes to our record keeping practices and office procedures, we decided to implement it first at one hospital and to phase in the billing process by running concurrently with the manual system until it was well proven. After eight months, we progressively added three more hospitals to the system. The system has been highly reliable; neither human error nor machine failure has ever caused more than a single record to be lost during three and one-half years of operation and entry of more than 50,000 cases.

Monthly computer costs are approximately $800 for processing 1800 cases, of which $450 is for data entry, $125 is for a disk storage space to archive the data, and the remainder is for producing reports and performing ongoing development. Records older than six months are infrequently referenced and are kept in off-line disk files to reduce storage costs. The system incurs no secretarial costs because data entry is less time consuming than our previous manual record-keeping procedures. However, system maintenance, enhancements, generating ad hoc reports, and performing on-line inquiry continue to consume a surprising 40–50 hr of the analyst's time monthly, suggesting that such systems should be written by in-house personnel, rather than by outside consultants. Our experience is consistent with reports that over the lifetime of a software package, typically 50% of the programming effort is expended in system enhancements and maintenance (11).

Although originally funded by the department without grant support, the system has unexpectedly become self-supporting, because previously lost professional fees in excess of $2000 monthly are now recovered when we check our computer-generated log against the operating room records. At the University Hospital alone, the office copies of approximately two anesthetics per month are misplaced, usually when high-risk patients bypass the recovery room and go directly to the intensive care unit.

We have found that our residents and others learn the coding scheme easily and only occasionally need to look up the mnemonic codes for unusual anesthetics. Copies of the codes and instructions for using the system are kept in each anethesia machine for ready reference. Approximately 10% of the anesthesia records are found to be incorrect or incomplete when first submitted, and these are returned promptly for correction and reentered by the following business day.

Discussion

Our system records considerably fewer data than the recently reported CAPE (1) system, because we have no preoperative data, and our intraoperative data collection has been held to a minimum. Nevertheless, we consistently find that about 10% of our records are incomplete or incorrect on first submittal, and although we have been able to reduce this figure temporarily by circulating reminders to clinical personnel, the rejection rate tends to return to 10% soon afterwards. Chase et al. (1) reported 98% reliability in clinician-recorded data on their preoperative form, but intraoperatively, the reliability (of recording intravenous fluid administration) was initially only 90.8%. The reliability increased to 97% through physician education, although it is not stated whether this improvement was sustained. Chase et al. also report a data entry error rate of 2%, and similarly, our audits find 1–2% of records in error. These observations support the importance of making the coding process as simple as possible, minimizing any extra effort required of clinical personnel, rewarding their efforts by providing them with useful information (such as the individual activity reports), and having the computer perform every conceivable check of the data on entry.

In contrast to the CAPE system, ours uses commercially available data base management software, rather than specially designed data structures, and our programs (except for the data entry program) are written in the programming language of the data base management system, rather than in Fortran or assembly language. Although we pay a considerable premium in processor time and disk storage space for using the commerical data base system, the programming effort was greatly reduced, and the resulting programs are far easier to understand and modify. What is more important, the data base management system allows us to generate ad hoc reports easily and to answer questions interactively from a terminal. We typically receive two requests for information per week from our departmental management, faculty anesthesiologists, our surgical colleagues, or the hospital administration.

Despite frequent queries from other departments, we have had only limited call to provide information services on a regular basis and thus share the data entry and computer costs. Some departments track surgical activity with their own computer data bases, duplicating to some extent our own efforts. However, their data bases have only a subset of the information that we collect, and they do not perform the extensive verification that we do. Having a single source for surgical data would offer clear advantages to all users, if the data processing department could integrate these data into a hospital-wide information system (12). Because the anesthetist in the operating room is in a unique position to gather accurate surgical data, we suggest that for surgical data systems of the future, anesthesia departments might be made responsible for data acquisition and verification, while the computing organizations be responsible for data archiving and dissemination.

In summary, we have developed a successful surgical data base that evolved from (less succcessful) earlier efforts at computerized case record collection in our department. We believe that the keys to the success of this system are 1) that it imposes minimal additional workload on the anesthetist, 2) that it employs extensive manual and computer verification of the data, 3) that it provides rapid feedback when errors or omissions are found, and 4) that it encourages faithful completion of the forms by providing essential services (such as billing) to the department and by providing useful information to all department members. In addition, the commercial data base management software facilitates maintaining and upgrading the system and allows for queries from the computer terminal as questions arise. These advantages have been well worth the additional computer costs.

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1985;64:432–51

Review Article

Ionized Calcium, the Heart, and Hemodynamic Function

Lambertus J. Drop, MD, PhD

The calcium ion is well known to be essential for myocardial contraction as shown more than 100 years ago by Ringer (139); more specifically, as first demonstrated by McLean and Hastings (109) in 1934, calcium increases the contractile force of the amphibian heart. Clinically, therapeutic use of calcium is common as shown by pharmacy statistics obtained at the Massachusetts General Hospital, where more than 30,000 ampuls and syringes of calcium are ordered for use in patients each year, on various indications. Calcium salts are positive inotropes (22,47,53), but they also influence vascular smooth muscle tone (74,77,121,167). Because the calcium ion is essential to contractility of vascular smooth muscle, the peripheral vasculature contributes importantly to the blood pressure changes that occur in patients with hypocalcemia (30,55,150,153) and hypercalcemia (60, 99,150).

The purpose of this paper is to present a current review on blood-ionized calcium ($[Ca^{2+}]$) measurement and its interpretation, on the cardiac and peripheral vascular actions of calcium, and on the usefulness and limitations of calcium replacement therapy. Although calcium channel blocking drugs are currently of great interest because of their important beneficial effects for the treatment of different cardiovascular disorders (6,13,21,136), this subject is not extensively discussed here.

Total vs Ionized Calcium

Calcium in the circulating blood is a source of extracellular calcium, which is thus available for action within the cell. This blood calcium is present in different forms: bound or complexed and free or ionized (Fig. 1). This division is of major physiological interest, for only the ionized form is physiologically active, as first demonstrated by McLean and Hastings in 1934 (109). These authors concluded that the ionized calcium was essential to rhythmical mechanical activity of the isolated perfused frog heart. More than four decades later this idea was confirmed in the dog heart when it was shown that, although simultaneous infusion of calcium gluconate and trisodium citrate increased serum concentrations of total calcium, ionized calcium levels and myocardial contractility (as measured by peak left ventricular *dP/dt*) decreased in parallel (22).

The pioneer work by McLean and Hastings also led to the development of a nomogram (110) that has become a cornerstone in the clinical evaluation of serum-ionized calcium concentrations. This nomogram allows the ionized calcium concentration to be derived when total calcium and total protein concentrations are known, assuming that pH equals 7.35 and the albumin:globulin ratio is 1.8. Presently, because direct $[Ca^{2+}]$ measurements are not always universally available in all hospital settings, this (110) or similar nomograms (156) form the basis for $[Ca^{2+}]$ level estimates in both surgical and medical patients. Thus total calcium levels are still widely used today to reflect calcium homeostasis. However, because considerable disturbances in ionized calcium balance may exist with normal total calcium values (25,51,94), physiological events are more appropriately related to ionized calcium. Its measurement is, therefore, emphasized as essential in the understanding of the hemodynamic consequences of hyper- and hypocalcemia.

Clinical $[Ca^{2+}]$ Determination

Plasma ionized calcium may be determined in two ways: indirectly, as a correlate of either total calcium

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Address correspondence to Dr. Drop, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

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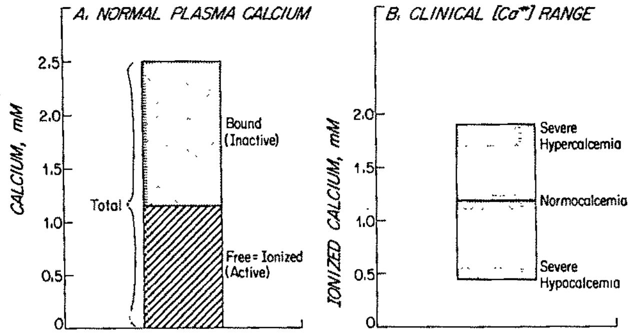

Figure 1. *Left panel*: normal ionized and total calcium concentrations. *Right panel*: clinically encountered ionized calcium levels. Data in (46), (56), (60), and (144).

by use of a nomogram (110,156) or as a correlate of the duration of the Q–T interval of the electrocardiogram (144,148); or directly, by use of a calcium-selective electrode system.

The indirect methods represent estimates only and, therefore, may or may not adequately reflect the calcium ion status in patients. In nomograms (110,156) used to derive ionized calcium, a predictable correlation between total and ionized calcium is assumed. But in several groups of patients, total and ionized calcium have been found to change independently, leading to a disparity between nomogram-predicted [Ca^{2+}] values and those directly measured (51,94). Although an inverse relationship between [Ca^{2+}] and the duration of the S–T segment of the electrocardiogram has been known for decades in patients with chronic disturbances in calcium equilibrium (23), acute alterations in calcium ion balance cannot be accurately determined by the Q–T interval (as a correlate of the duration of the S–T segment), as shown clinically (73,144) and experimentally (148). Only direct [Ca^{2+}] measurements by electrode can provide a conclusive picture of the calcium ion status in patients, which is necessary in patient management.

Calcium Electrode System

Like some other frequently measured electrolytes (sodium, potassium, and hydrogen ions), calcium ion activity in specimens of whole blood, plasma, serum, and aqueous solutions can be measured readily by electrode systems that are made highly selective for one ionic species. A detailed description of ion-selective electrodes is outside the scope of this review, but general concepts of electrode design and function will be discussed here.

A calcium ion-selective electrode system consists of a measuring electrode that contains an ion-selective membrane and an external reference electrode; both are connected to an expanded scale voltmeter with a high input impedance. Because both electrodes are also in contact with an electrolyte containing sample solution, the system is like an electric circuit.

Any ion-selective membrane generates a membrane potential. The diffusion potential that is formed with unequal diffusion rates of the electrically charged components of an electrolyte was described more than a century ago (123,127). Membrane electrochemistry was founded in 1890 (127) with the concept of the semipermeable membrane, i.e., the membrane that is permeable to certain ions and not to others. A membrane theory of the electrical properties of cells and tissues was advanced at the turn of the century (15); it still is the basis of current concepts of bioelectric potentials today. The study of compact solid membranes brought the discovery of hydrogen-selective glass, which led to the development of pH electrodes in the 1920s. Their theory and practical applications are now well established. A calcium electrode was developed as early as 1898 (105); several other electrodes that proved to be of limited usefulness were developed within the last five decades (1,64,164). These electrodes suffered from limited selectivity and poor stability in protein-containing solutions. The calcium electrode that held promise for use in biological media was developed in 1967 (141,142).

A feature that the calcium-selective electrode has in common with the pH electrode is the mechanism of ion exchange, which involves ion transfer across the membrane phase boundary at its interface with the bathing solution; for this process it is important that membrane and bathing solution phases be immiscible.

The calcium-selective membrane with mobile-ion selective sites separates two inorganic aqueous calcium solutions: one, a calcium chloride solution of known and constant composition (10^{-1} M) called the internal filling solution in which a silver chloride-coated silver wire (internal reference element) is positioned and the other, the sample solution in which the calcium ion activity is to be measured in the presence of other ions (Fig. 2). The calcium electrode developed in 1967 (14) and successful for clinical use is of liquid membrane design, i.e., the calcium-selective membrane actually is a thin sheet of a viscous water-immiscible organic liquid, held in position by an inert porous cellulose membrane or incorporated in inert material. The organic liquid contains calcium di(n-decyl)phosphonate in the organic solvent dioctylphenylphosphonate (142) (insert, Fig. 2). Other high molecular weight organophosphorus compounds and solvent mediators (112,115,116,166) and inert substances to incorporate the liquid ion exchanger such

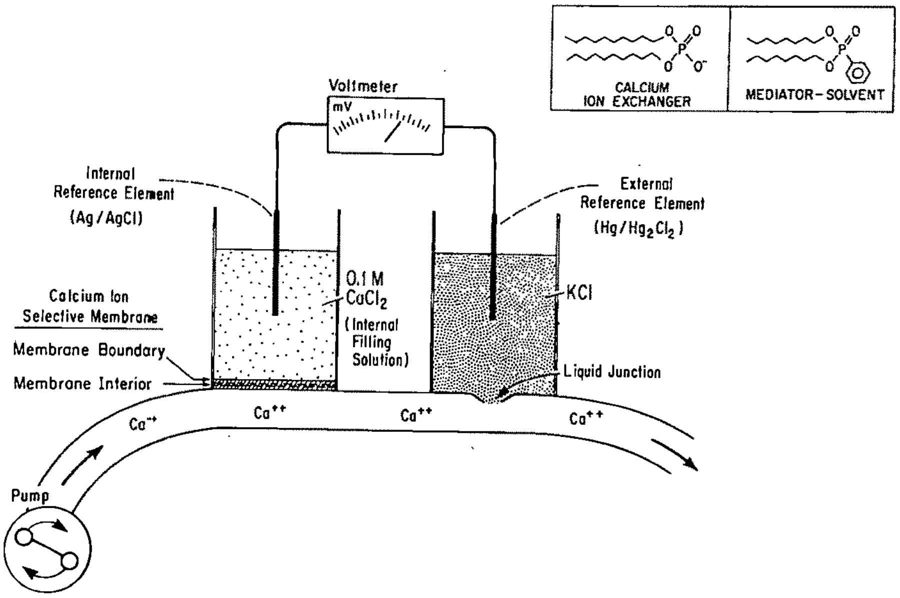
CALCIUM ION EXCHANGER
MEDIATOR-SOLVENT
Voltmeter
mV
Internal Reference Element (Ag/AgCl)
External Reference Element (Hg/Hg$_2$Cl$_2$)
0.1 M CaCl$_2$ (Internal Filling Solution)
KCl
Calcium Ion Selective Membrane
Membrane Boundary
Membrane Interior
Liquid Junction
Ca^{++}
Ca^{++}
Ca^{++}
Ca^{++}
Pump

Figure 2. Diagram of a calcium-selective electrode system. The calcium-selective membrane separates the sample solution from the internal filling solution, in which calcium ion activity is constant. The reference electrode completes the circuit. A pump provides slow, constant flow of the sample in which calcium ion activity (Ca^{2+}) is to be measured. The calcium ion exchanger and mediator solvent, described in (112) and (241), are shown in the insert.

as poly (vinyl chloride) matrix have been explored; the resulting electrodes demonstrated improved ion selectivity (115,117,147). The electrode design was also simplified (147).

Within each phase, in the aqueous solutions and in the membrane, there is electroneutrality; i.e., there is an equal number of positive and negative charges. In contrast, at the interface of the organic membrane and inorganic electrolyte solutions, the charge equilibrium is disturbed, because whereas the calcium ions in the membrane are free to exchange with calcium ions in the aqueous phase, the organophilic phosphonate ions are limited to the membrane phase because in water they are insoluble and immiscible (28). The thickness of the membrane is sufficient to provide an inside region and two boundary surfaces that separate the membrane from the exterior phases (28), and calcium ion transport occurs from the aqueous phase into the boundary of the membrane phase where the calcium ion loses its hydrated layer and complexes with the organophosphate sites. However, the total number of transported calcium ions is infinitesimal relative to the number present in even the most dilute sample (142). The transported calcium ions complex with the organic phosphate binding sites and the so-complexed organophosphate molecules move down a concentration gradient leading to a charge separation between the membrane boundary interfacing with the internal filling solution and the boundary interfacing with the sample solution; and a membrane potential difference develops. The movement of calcium phosphonate complexes toward the membrane interior continues until no further organophosphate sites are available for calcium ion binding with a decrease in electrode slope, which indicates that the electrode should be replaced.

Although it is the calcium-selective membrane of the calcium-measuring electrode that determines the potential generated by the calcium ion in the sample, this potential cannot be measured without an external reference electrode. It consists of a mercurous chloride-coated mercury (Hg/Hg_2Cl_2) element, positioned in a concentrated (3 M or higher) KCl solution (Fig. 2), to generate a chloride ion potential, which contributes to the recorded electrode potential. There are two other contributing potentials; the first is derived from the internal reference element and the second is a liquid junction potential generated between the potassium chloride (external reference) solution and the sample solution. This potential develops because the ions present in these two solutions diffuse at different rates (11).

The calcium ion activity in the internal filling solution maintains a stable potential between the silver–silver chloride internal reference electrode and the inside membrane surface and the chloride ion provides stable internal and external reference element potentials (142); the junction potential is constant as long as a steady state is maintained at the boundary between reference and sample solutions (11). Changes in the recorded total electrode potential, therefore, reflect the calcium-ion activity in the sample solution, as determined by the Nernst equation. Electrodes currently in clinical use perform according to these theoretical expectations, even in complex biological media such as plasma or whole blood.

Because the electrode potential is an interface phenomenon, the response time of ion-selective electrodes is closely related to the speed with which the calcium ions in the thin film of aqueous sample solution in the immediate vicinity of the membrane exchange with those in the membrane, making a flow-through design as used in several commercially available calcium ion instruments particularly useful (112). Essential to the appropriate performance of the entire electrode system is an adequate voltmeter sensitivity and electrode stability. For example, a 1-mV error in electrode potential leads to an 8% error in measured calcium ion activity (117).

Ion Selectivity

Ideally, the calcium electrode should respond only to the activity of calcium ions in the sample, i.e., the calcium electrode should be calcium-specific. But the electrode is ion-selective. The presence of other cations, therefore, imposes limitations to the sensitivity of the electrode toward the calcium ion. This is a problem in biological media such as blood, which represents a mixed electrolyte solution also containing proteins in which sodium ion activity is about 150 times that of calcium. The degree to which an electrode potential represents a particular ion in preference to another is expressed by selectivity constants. When the selectivity constant for cations other than calcium is high, the electrode response to these cations is minimal (119). Generally, selectivity constants are estimates, influenced by the ion exchanger, its organic solvent, the matrix used to support the membrane, and total ionic strength of the sample (117). For example, one calcium electrode has a selectivity constant for sodium of 10^4 (141). The electrode thus responds to calcium in preference to sodium by a factor of 10^4, but the sodium-induced error is also determined by its activity and by ionic strength as discussed below. Another calcium electrode, manufactured by incorporation of the same liquid calcium ion exchanger in a poly (vinyl chloride) matrix membrane, has a sodium selectivity constant of 8.7×10^5 (147).

Hydrogen ions interfere with calcium ion measurement but only at pH values at or below 5.5 (141) or 6.0 (147), which is well below the physiological pH range, and thus a pH-induced interference with calcium ion measurement is not of clinical concern. However, within the physiological pH range, changes in pH do cause [Ca^{2+}] changes in blood or plasma samples, probably secondary to pH-induced changes in the affinity of protein for the calcium ion as mentioned below. Therefore, the calcium ion measurement is performed without carbon dioxide loss to prevent secondary pH changes. Interference by potassium or magnesium ions with calcium ion measurement by several different calcium electrodes is small to negligible because of high selectivity constants and low activities of these ions (112).

Activity vs Concentration

Ions in very dilute solutions are considered to behave like gas molecules, but this parallel does not apply at higher concentrations, primarily because of interionic electrostatic interactions that limit free movement. Determination of vapor pressure, conductivity, and freezing point depression have confirmed the idea that the apparent number of free ions (activity) in solutions is less than calculated from molar concentrations, assuming complete dissociation of salts (75). The apparent number of independent ions is referred to as ionic activity, which is related to concentration by the formula

$$A = \gamma \cdot C,$$

where A is the activity, γ is the activity coefficient, and C is the molar concentration. At infinite dilution, γ equals 1.

Ion-selective electrodes respond to ionic activity rather than concentration. Hence, activity standards would be necessary for electrode calibration. Preparation of such standards requires knowledge of the activity coefficient of the calcium ion (10). But there are two problems. First, the activity of one single ion in solution cannot be determined without the presence of the corresponding anion. Rather, as an approximation and by convention, the calcium ion activity is calculated from the mean ionic activity coefficient of the electrolyte $CaCl_2$ (75). Second, because the most important variable influencing activity coefficient is ionic strength (97,118), sodium chloride is added to the calcium calibration standard to make its ionic strength similar to that of plasma, and that alteration has its own influence on the calcium ion activity in the calibration standard. Therefore, calcium electrode calibration standards are prepared with analytical reagent grade crystalline $CaCl_2$ carefully weighed and dissolved is distilled deionized water and [Ca^{2+}] is expressed in terms of millimolar (mM) concentration.

In the analytical cycle of the calcium electrode system, calcium standard calibration and plasma solutions move past the electrode in sequence allowing the [Ca^{2+}] in both solutions to be compared. The adjustment of ionic strength of the calcium calibration standard with sodium chloride eliminates a parasite potential of unpredictable magnitude that would develop if calibration standard and plasma solutions were of grossly unequal ionic strength (57). In view of this, urine specimens are not suitable for [Ca^{2+}] measurement by electrode.

Variations in ionic strength from one plasma sample to another are very small except under conditions of extreme degrees of hypernatremia or hyponatremia. For example, a decrease in Na^+ by 28 mM leads to a decrease in measured [Ca^{2+}] by approximately 0.04 mM, and an increase in Na^+ by the same amount leads to an increase in measured [Ca^{2+}] by approximately 0.04 mM (93).

Laboratory Use of the Calcium Electrode

In the clinical laboratory, instrument calibration is performed with solutions of different [Ca^{2+}] concentrations bracketing the [Ca^{2+}] in plasma; and thus the relation between standard-generated millivoltages and [Ca^{2+}] concentration (mM) is established. The sample-generated millivoltage is then determined and its value interpolated on the calibration curve to give a result in mM. The difference between the millivolt readings obtained with two calibration standards must be within a predetermined range for adequate electrode performance. The calcium electrode system (NOVA Biomedical) in use at the Acute Care Laboratory of the Massachusetts General Hospital incorporates three different ion-selective electrodes (sodium, potassium, and calcium); it also performs the calibration, slope check, and interpolation procedures automatically. The system is also thermostated to eliminate errors related to difference in temperature at which the [Ca^{2+}] is measured and at which [Ca^{2+}] is present in the patient. Another attractive characteristic is that the required sample size is small (300 μl), a real advantage for samples obtained from pediatric patients; however, it should be remembered that with a small sample size the ratio between syringe dead space and sample blood volume is unacceptably high. This consideration is of practical importance because blood samples are clinically anticoagulated by prefilling the syringe dead space with heparin solution. The instrument is also equipped to aspirate and transport the sample to the sensing electrode, and the analytical result is digitally displayed within 90 sec after sample aspiration.

The lower limit of detection is determined by the solubility of the ion exchanger in the medium in which [Ca^{2+}] is to be measured. Several commercially available calcium electrode systems have a useful sensitivity range of 10^{-5}–10^{-1} M (91,116).

A problem with electrode measurements in general is electrode drift with passage of time. Easiest to correct is a unidirectional parallel drift, i.e., a shift of the calibration curve without a change in slope, by recalibration of the electrode system. Thus the NOVA instrument is recalibrated every four hours. Liquid membrane electrodes may also display a calibration curve shift together with a change in slope, i.e., the calibration curve pivots around some intermediate point but without a predictable pattern. Whenever the slope falls below a critical level, an error code is displayed by the NOVA instrument. Electrode replacement may be required to correct the problem. The most frequent causes of electrode drift are temperature gradients between the sample (which may have been placed on ice) and the electrode, which is minimized by thermostating the electrode system. Other sources for electrode drift are an unstable liquid junction, pressure variations (owing to partial or complete blockage of the fluid lines of the flow-through system) with or without loss of membrane integrity, depletion of liquid ion exchanger and deposition of plasma proteins, clots, or debris at the membrane. Deposition of plasma proteins is a problem because at physiological pH, proteins display cation exchange properties. The flow-through design with passage of aqueous solutions after passage of plasma or whole blood serves to minimize this problem. Pressure variations can easily occur with blood in a system of narrow tubing, but they can be minimized by appropriate instrument maintenance procedures at regular time intervals and by appropriate anticoagulation of blood samples.

Our experience indicates that electrodes that measure Na^+, K^+, and [Ca^{2+}] have a life span of the order of three weeks during which time approximately 4000 blood and aqueous samples are analyzed. Comparative cost analysis of [Ca^{2+}] measurement by electrode is impossible because [Ca^{2+}] cannot be measured by other analytical techniques readily available in the clinical laboratory. We find the [Ca^{2+}] analysis by electrode easy, fast, and reproducible, but familiarity of the laboratory technical staff with electrode measurements in general and electrode malfunction troubleshooting procedures are essential. Most of our specimens are whole blood rather than serum or plasma, because the results are needed within minutes after withdrawal of the blood sample for clinical decision making.

A correlation between [Ca^{2+}] and clinical response is observed primarily in the clinical hypocalcemia range when left ventricular pump performance decreases with decreasing [Ca^{2+}] levels. With severe hypocalcemia, there is arterial hypotension that relates to both cardiac and peripheral vascular function. The relationship between $[Ca^{2+}]$ and clinical response in the hypercalcemia range is subtle. Both relationships are discussed in detail in the sections that follow; the correlation with cardiac performance is illustrated in Figures 4 and 5.

Interpretation of $[Ca^{2+}]$ in Patients

To interpret $[Ca^{2+}]$ measured in patients, comparison is made with a reference $[Ca^{2+}]$ value. However, this reference (normal mean) $[Ca^{2+}]$ value has been a source of major concern because of its variation over a relatively wide range (mean values ranging from 0.96 (152) to 1.27 mM (93)). Such a range is not compatible with the concept of calcium ion concentration being among the most tightly regulated physiological variables, as proposed by McLean and Hastings (109). Recent reports have pointed to the need for attention to detail in the technique of $[Ca^{2+}]$ measurement and uniformity of sample handling, thereby reducing but not eliminating the spread of normal mean $[Ca^{2+}]$ values (52,56).

In the evaluation of $[Ca^{2+}]$ in patients, several details of $[Ca^{2+}]$ measurement are of interest because of their ability to modify the analytical results. An important factor is the particular calcium-selective electrode system used for $[Ca^{2+}]$ determination (19,56). Although different available calcium electrode systems have the technology in common, a measurable difference in apparent $[Ca^{2+}]$ has been documented with use of instruments of two different manufacturers. For example, the normal $[Ca^{2+}]$ established with one instrument was 1.12 ± 0.01 mM (mean ± SEM), whereas this value was 1.22 ± 0.01 mM using another. Near the upper limit of the clinical hypercalcemia range there was a 15% difference in results produced by these two instruments (56).

Another factor is pH. Because alterations in pH in protein-containing solutions are associated with measurable changes in calcium ion activity, the analysis of $[Ca^{2+}]$ is performed by anaerobic introduction of the sample of blood, plasma, or serum into the electrode to prevent carbon dioxide loss and secondary changes in pH. In anesthetized patients with a change in pH from 7.6 to 7.2, $[Ca^{2+}]$ increased on average by 0.20 mM (32,52,107). This small pH effect may be attributed to competition between hydrogen and calcium ions for protein binding sites (119).

Third, plasma protein concentrations are important because protein represents the chief binding substance of calcium in plasma. The difference between total calcium (approximately 2.5 mM) and ionized calcium (approximately 1.10 mM, see Fig. 1) is explained primarily by protein binding. The clinical importance of protein affinity for calcium is illustrated by the observation that transient lowering of $[Ca^{2+}]$ occurs in recipients of processed albumin solutions infused at a rapid rate (82).

Heparin, which can lower $[Ca^{2+}]$ both by the negative charge on the heparin molecule and by dilution of the specimen by the heparin solution, is not of clinical concern as long as heparin concentrations remain below 10 units/ml whole blood (52). Thus $[Ca^{2+}]$ measurement can be performed in serum, plasma, and whole blood. The site of blood sampling (arterial or venous) for $[Ca^{2+}]$ determination seems unimportant because the $[Ca^{2+}]$ difference across the systemic vascular bed is insignificant over the clinical range of $[Ca^{2+}]$ (52).

Calcium and the Heart

Cardiac Pacemaker Activity

In all cardiac cells, the interior is separated from the extracellular fluid by a phosphobilayer membrane in which, according to a current model, specific protein subunits function as ion-selective channels; each channel more or less specifically controls the passage of sodium, potassium, and calcium ions (88,90,157). With these ion channels, the cell membrane exerts a tight control over the ion distribution on both sides of the membrane. This leads to a voltage difference, which is measurable as a membrane potential between the interior of the cell and extracellular fluid. A cycle of opening and closing of the ion-selective channels leads to a sequence of ionic translocations across the cell membrane, resulting in its depolarization and electrical activation (88). Subsequent ionic movement, including potassium efflux out of the cell, returns the membrane potential to its resting state (40,151). Designations of transmembrane ionic currents include the direction (inward or outward) and the ionic charge carrier (sodium, potassium, calcium, or chloride ions). Voltage-dependent changes in transmembrane currents during depolarization and repolarization phases can be recorded as cardiac action potentials that vary from one region of the heart to another. Thus their shape, amplitude, and duration differ in different areas of the heart. For example, in sinoatrial and atrioventricular nodal cells the action potential appears as a slowly rising low amplitude plateau that is primarily dependent on calcium (slow inward) current (40,128). Therefore, the calcium ion is crucial for cardiac automaticity. In Purkinje and ventricular muscular fibers the general characteristics of the action potential are a rapid depolarization (up-

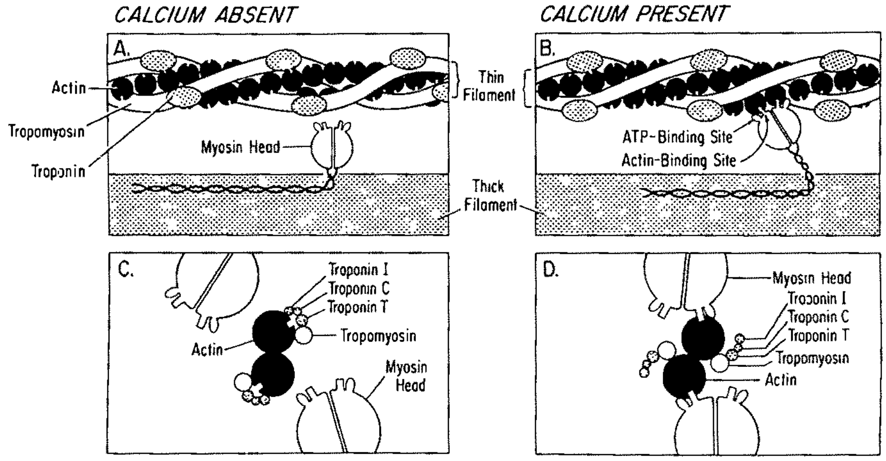

Figure 3. Schematic drawing of possible mechanism of interaction of contractile proteins in the absence (*panels A and C*) and presence (*panels B and D*) of calcium. According to this model, in the resting muscle (*panels A and C*), the troponin complex is positioned such that interaction between actin and myosin head is prevented. In the presence of calcium (*panels B and D*), there are interactions between the proteins of the thin filament with reposition of the troponin–tropomyosin complex, allowing binding of myosin heads to actin binding sites. (*Panels A and B*) Longitudinal view of model, adapted with permission from (120); (*panels C and D*) cross-sectional view of model, adapted with permission from (86).

stroke) followed by a longer lasting plateau (85,159). This plateau represents the balance of a slow inward current and outward potassium current that terminates the depolarization.

Two currents distinguishable by the different response of the conductance mechanism to different blocking drugs contribute to the inward current. First, there is a fast inward current, produced by sodium influx, which corresponds to the initial spike of the action potential (40,159). Second, there is a slow inward current, which is principally characterized by influx of calcium during the plateau phase of the action potential (124,138). Thus the calcium ion is essential to conduction and myocardial contraction (85,138). If the extracellular calcium level decreases to zero, the slow inward current is carried by the sodium ions (137). Calcium efflux occurs by two principal mechanisms: the sodium calcium exchange (122) and the calcium pump (88). Both mechanisms require the splitting of ATP to maintain a 10,000-fold calcium ion gradient across the cell membrane (88).

Excitation–Contraction Coupling

Entry of calcium ions during the plateau phase is important for the linkage between excitation and contraction in myocardial muscle cells (124). Thus the calcium ion is an essential coupling factor between events at the cell surface (depolarization) and interior (contractile apparatus). Excitation–contraction coupling in cardiac muscles depends on a rapidly exchangeable calcium pool (95,96), and therefore the contraction of myocardial fibers is critically dependent on extracellular calcium sources. This phenomenon was first shown by Ringer (139), who found that contractions of the isolated frog heart disappeared within seconds after perfusion with a calcium-free solution.

Calcium is a universal coupling factor between excitation and response in many different types of cells (9,146). Calcium, therefore, is also a key factor in the linkage between membrane depolarization, for example, and synthesis and release of intracellular second messengers hormones as well as enzymes. Thus calcium controls secretion and release of insulin (44,49), aldosterone (125), vasopressin (145), prostaglandins (42), renin (38), and neurotransmitters (50,143). A decrease in calcium flux is, for example, associated with decreased release of insulin (49). Calcium also activates enzymes of the coagulation cascade (71), and plays a central role in the mechanisms of action of hormones (12,14,65,146) and different classes of drugs (6,100,176).

Intracellular Calcium–Protein Interaction

Four major proteins participate in the contractile process: the contractile proteins actin and myosin, and the regulatory proteins troponin and tropomyosin (58). Troponin consists of three subunits: troponin T, troponin I, and troponin C. According to a model of the interaction of calcium with the contractile apparatus (Fig. 3), calcium binds to troponin C (which is the calcium receptor protein on the myofibril) and the myosin binding site of actin is exposed (86,120). Utilizing energy supplied by hydrolysis of ATP, actin slides past the myosin filament, and the sarcomere shortens or tension develops (83).

The amount of free calcium present in the cytoplasm is a major determinant of the adequacy of calcium ion delivery to the contractile proteins; this factor can therefore be related to the rate of tension development and total tension developed (96). This relation has been demonstrated in cardiac myofibrils in which the sarcolemma is removed (61,62) so that the sarcoplasmic reticulum remains intact and yet directly accessible by externally applied calcium ions. In such a preparation no tension is developed (i.e., myosin–actin interaction is absent) at [Ca^{2+}] of 10^{-7} M, and maximum tension (maximum myosin–actin interaction) is achieved at [Ca^{2+}] of 10^{-5} M. But the calcium ion concentration in blood (and therefore, also presumed in the extracellular fluid) is on the order of 10^{-3} M. Thus as mentioned, the calcium gradient across the cell membrane is between 100- and 10,000-fold, depending on the state of electrical activation.

Crucial to stimulation of the contractile apparatus is the transient increase in cytosolic calcium that occurs principally by three mechanisms: by influx of calcium ions from extracellular sources during the plateau phase of the cardiac action potential (5,137); by calcium release from the intracellular calcium stores (40); and by sodium–calcium exchange (122).

Of these mechanisms, calcium release from intracellular stores is most important because the amount of transmembrane flux with each beat is insufficient to activate the contractile apparatus. Thus the transmembrane flux acts to increase cytosolic calcium concentration, which triggers the release of calcium from stores, located primarily in the sarcoplasmic reticulum (62). The instantaneous relation of the intracellular myocardial ionized calcium transient and muscular tension development can be demonstrated in mammalian heart cell preparations using aequorin as a photosensitive protein (4,140).

Muscular Relaxation

The calcium binding to troponin C is reversible; thus relaxation occurs when the calcium ion is dissociated from the troponin binding site. This dissociation occurs when the free [Ca^{2+}] in the cytosol decreases both as a result of sequestration of calcium in the storage sites (63) and as a result of extrusion of calcium from the cell (2,122). The removal of calcium from the contractile sites requires ATP splitting and thus is an energy-consuming process (88). In the presence of energy deficiency, therefore, relaxation is impaired (18,72,102,130).

Role of Cyclic AMP in Excitation–Contraction Coupling

Besides the calcium ion, the cyclic nucleotide adenosine 3:5 monophosphate (cyclic AMP) is essential as a second intracellular messenger in the contractile process (135). Calcium and cyclic AMP are interrelated (87,165): calcium regulates the rate of cyclic AMP synthesis and breakdown, while cyclic AMP controls calcium ion influx into the cell as shown by a calcium inward current that is observed with intracellular application of cyclic AMP (131). Cyclic AMP also controls intracellular uptake and release of stored calcium and thus, the contraction relaxation cycle (178).

The current view is that in cardiac muscle, oxidative phosphorylation is required for activation of the slow calcium channels and calcium flux (88). Calcium then acts through phosphorylation of several intracellular organelles including sarcoplasmic reticulum and myofibrils. This response is mediated by a system of adenylate cyclase, cyclic AMP, and protein kinase (168). Depression of slow channels secondary to insufficient energy supply with decreased calcium flux can explain decreased contractility that occurs with ischemia secondary to coronary artery occlusion (159), although other mechanisms have been advanced (92).

Calcium as a Mediator of Action of Drugs and Hormones

The essential role of calcium flux in the rhythmic contractile activity of cardiac and smooth muscle cells is evident from a hypocalcemia-induced decrease in contractility of both myocardial (22,53) and peripheral smooth muscle fibers (79,99,150,153). In contrast, although calcium channel blockers impede calcium entry during the plateau phase of the action potential (7,21) with an expected lesser tension generation or force development, the occurrence of these changes depends on the specific calcium blocker and the contractile tissue (167). For example, nifedipine decreases contractility of cardiac and vascular smooth muscle, whereas decreased cardiac contractility is hardly measurable with lidoflazine in therapeutic doses (168).

Other drugs that depend on calcium flux for their action include digitalis glycosides, sympathomimetic amines, and anesthetic drugs. The current concept of the mechanisms of digitalis action is that digitalis is associated with either interference with the enzyme essential to sodium pumping activity, with a resulting decrease in the amount of calcium pumped out of the cell (3), or a derangement of sodium–calcium exchange (96). Both mechanisms result in increased intracellular calcium pool and thus increased interaction of calcium with the contractile elements. The β-adrenergic agonists augment the calcium influx by increasing the number of functional calcium channels (100). The α-adrenergic stimulation with norepinephrine produces peripheral vasoconstriction secondary to increased calcium entry and increased calcium mobilization in vascular smooth muscle cells (169).

Inhalation anesthetics depress myocardial per-

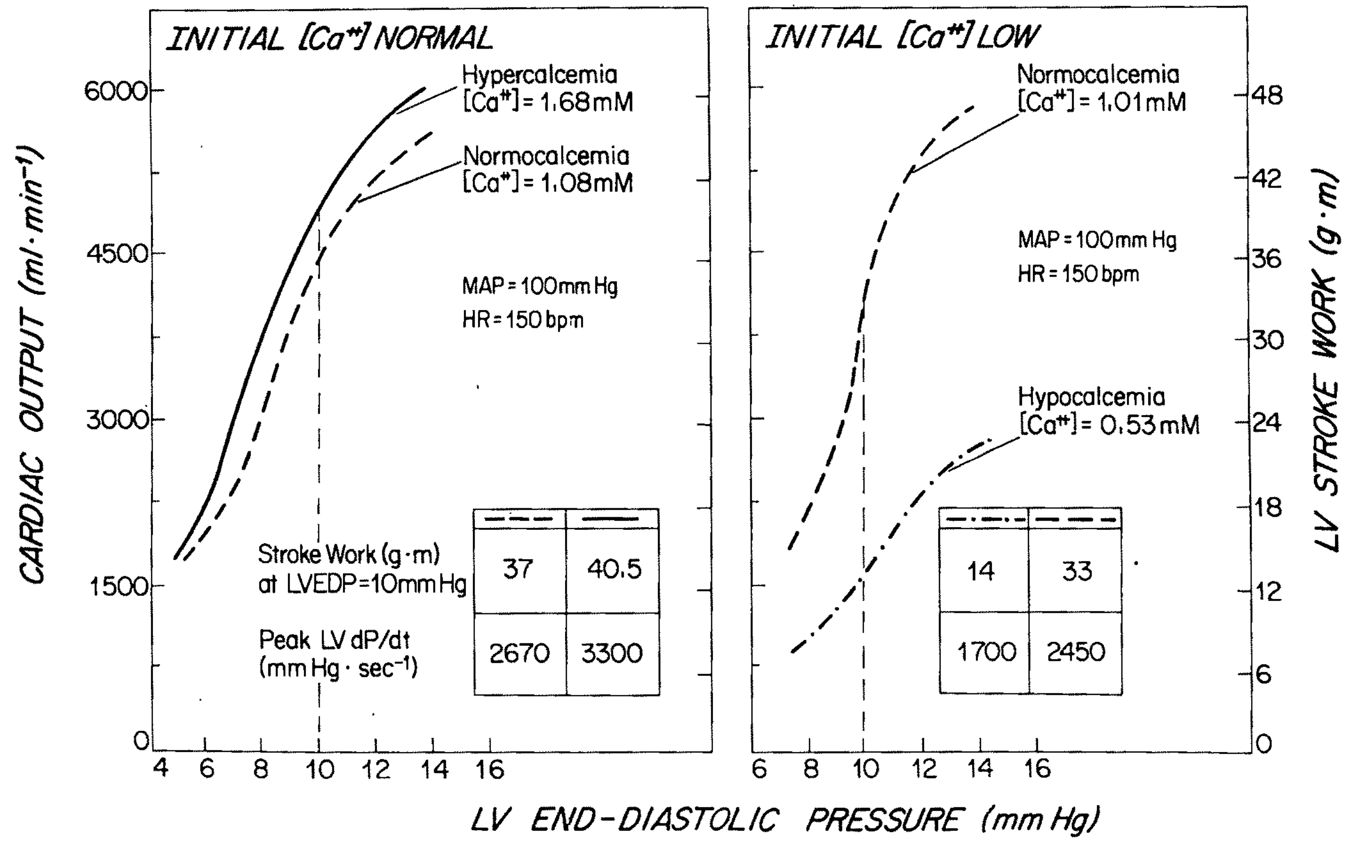

Figure 4. Disparity between force and velocity indices of left ventricular (LV) performance and the influence of initial [Ca^{2+}] on LV response to calcium that was infused continuously to produce different stable [Ca^{2+}] levels such that all data points of each curve were obtained at the same [Ca^{2+}]. These stable [Ca^{2+}] levels were also present in experiments illustrated in Figure 5. Curves obtained in the ejecting dog heart at constant mean arterial pressure and heart rate. *Left panel*: with initial normocalcemia (dotted line), calcium infusion, producing hypercalcemia (solid line), is associated with a small left and upward shift of the curve, and peak LV *dP/dt* (obtained at constant mean aortic pressure, cardiac output, and heart rate) increases ($n = 13$). *Right panel*: with initial hypocalcemia, calcium infusion is associated with a much greater shift of the curve to the left and upward, although the increase in peak LV *dP/dt* is similar to that seen in the left panel ($n = 10$). Mean hypo-, normo-, and hypercalcemic values are shown. All curves are schematically drawn on the basis of experiments with at least five data points. Mean values for stroke work at LVEDP = 10 and for peak LV *dP/dt* are given in the insert. Abbreviations: MAP, mean aortic pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure. Data in (53).

formance (24,154). For example, halothane depresses left ventricular (LV) pump performance as shown by decreased cardiac output at any end-diastolic pressure (154). Halothane also depresses regional myocardial shortening and decreases peak LV *dP/dt* (103). Similar effects have also been demonstrated with enflurane, halothane, methoxyflurane, and nitrous oxide in the decreased force development in papillary muscles (24,133).

Several mechanisms for the development of halothane-induced myocardial depression have been suggested. First, halothane in clinical concentrations decreases calcium influx through the calcium-selective channels (106). Second, halothane may also affect sarcoplasmic reticulum uptake and release of calcium (106,113,163); its extent seems to depend on intracellular ATP levels (133). Both these mechanisms interfere with calcium delivery to the contractile elements. Consistent with the idea that anesthetics interfere with calcium delivery to the contractile proteins is the observation that calcium bolus injection, resulting in increased extracellular calcium levels, reverses anesthetic-induced depression of papillary muscle contractility (132). This is of clinical interest because responses to exogenous calcium in patients anesthetized with potent inhalation anesthetics that depress cardiac function (47) differ from those observed in patients anesthetized with anesthetics that minimally affect cardiac contractility (60).

[Ca^{2+}] and Cardiac Function

The use of calcium salts in anesthesia may be illustrated by operating room statistics obtained at the Massachusetts General Hospital, where the pharmacy orders approximately 7500 ampuls and syringes of calcium (chloride and gluconate salts combined) for use during surgical operations each year. Of these,

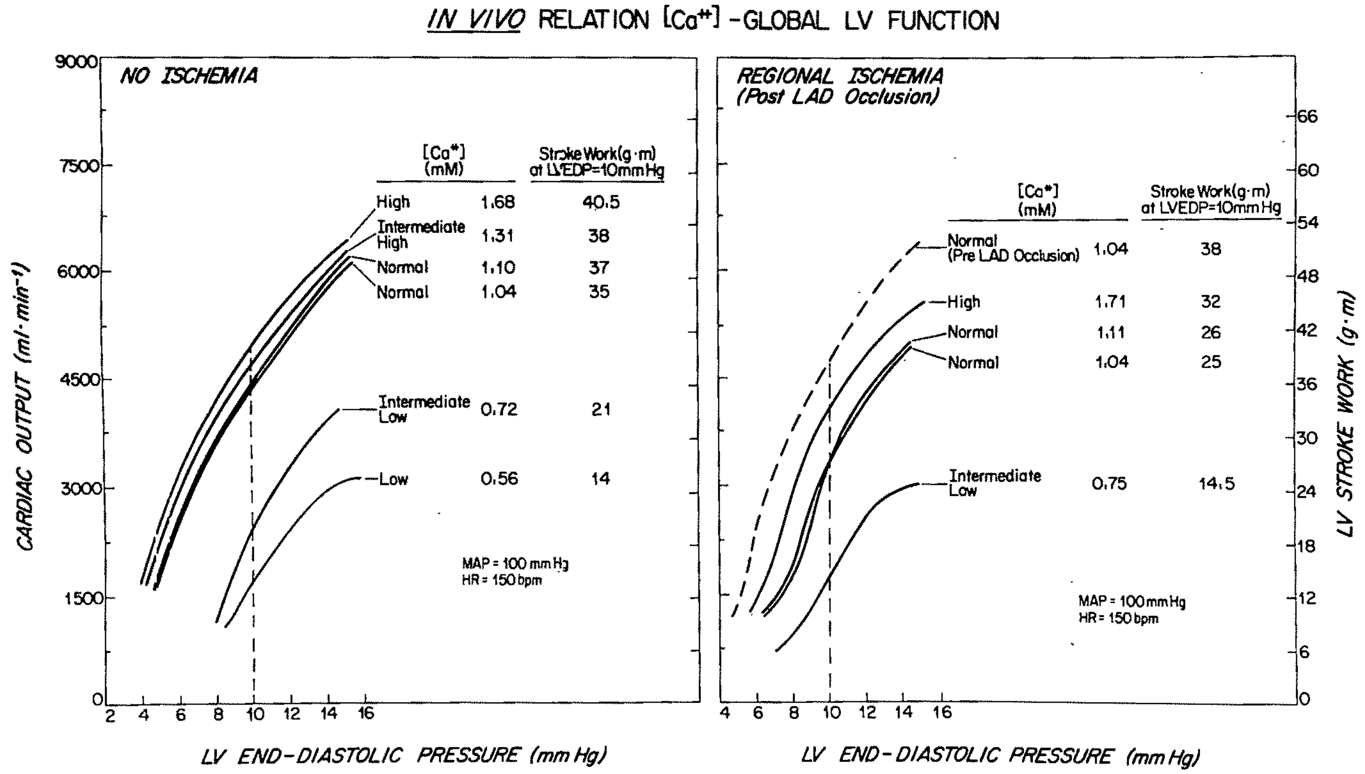

Figure 5. In vivo relation between [Ca^{2+}] and LV pump function obtained in the ejecting dog heart at constant mean aortic pressure and heart rate. *Left panel*: in the normal dog heart (no ischemia) different hypercalcemia levels (intermediate level, *n* = 3) produce a small displacement of the curve to the left and upward, whereas with different degrees of hypocalcemia, curves are displaced to the right and widely separated (intermediate high and low levels, *n* = 3; normal, high, and low levels, *n* = 13). *Right panel*: regional ischemia (secondary to acute left anterior descending [LAD] coronary artery ligation) in the dog heart produced a right and downward shift of the LV function curve, which is displaced to the right with hypocalcemia and to the left with hypercalcemia, but the preligation position is not achieved (*n* = 22). The preligation curve is marked by the dotted line; all postligation curves are marked by the solid lines. All curves are schematically drawn on the basis of experiments with at least five data points. In each panel, mean values of stroke work at constant LVEDP are given for each mean [Ca^{2+}] value. The sequence of different [Ca^{2+}] levels (as indicated in the key of each panel) in different dogs was randomized. Data in (53) and (68). Abbreviations are as in Figure 4.

approximately 2500 are ordered for patients during cardiac operations (approximately 1200 each year) and 5000 for patients undergoing other operations (approximately 20,000 each year).

Although the general limitations of extrapolation of experimental data to humans should be recognized, calcium-induced hemodynamic and cardiac changes recorded in dogs correspond well with those in humans. Therefore, observations in the dog importantly contribute to an understanding of calcium effects in the human.

It has been long known that calcium bolus injection is associated with increased myocardial contractility, where contractility is measured by peak LV *dP/dt*. For example, $CaCl_2$ bolus injection in the intact anesthetized dog produced a substantial increase in peak LV *dP/dt* (111,155) and in the open-chested dog, peak LV *dP/dt* correlated with [Ca^{2+}] over a whole range of [Ca^{2+}] values (22). But the clinical utility of this correlation is very limited for two reasons. First, peak LV *dP/dt* is not readily measured in patients. In contrast, cardiac pump function, i.e., that aspect of cardiac function that is essential to cardiac output and thus to organ perfusion, is readily assessed in patients from variables obtained by flow-directed balloon-tipped pulmonary arterial catheters. In the operating room and intensive care unit, LV pump function is expressed in terms of cardiac output or work as related to end-diastolic pressure. The second limitation of peak LV *dP/dt* as an index of myocardial contractility is that it is an index of velocity of myocardial fiber shortening recorded in the isovolumic phase of systole (172), and changes in peak LV *dP/dt* do not predictably correlate in a quantitative manner with force indices that denote pump function and are recorded in the ejection phase of systole. As a matter of fact, with positive inotropic interventions (e.g., catecholamines (16,41)), but also with negative inotropic interventions such as myocardial infarction (129), there is a disparity between velocity as indexed by peak LV *dP/dt* and force as indexed by LV function curves. Such a disparity also occurs with calcium, as shown

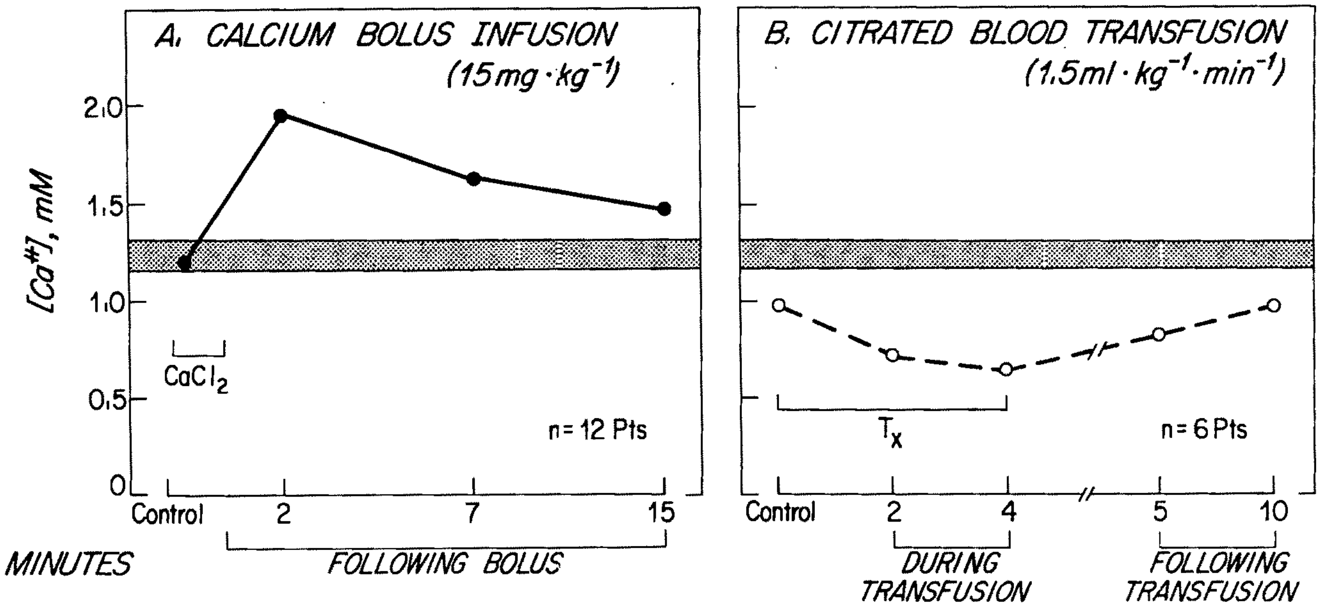

Figure 6. *Left panel*: transient hypercalcemia with $CaCl_2$ bolus infusion (15 mg·kg^{-1}) to 12 patients after separation from cardiopulmonary bypass. Data points represent mean values. Note the rapid decline of [Ca^{2+}] values even with the high dose infused. Data in (60). *Right panel*: transient hypocalcemia with citrated blood transfusion at a rapid rate (1.5 ml·kg^{-1}·min^{-1}) in 6 patients. Data points represent mean values. Note the rapid return of [Ca^{2+}] towards normal without calcium replacement therapy. The shaded area represents the 95% confidence limits. Data in (162).

in Figure 4. In the left panel, LV performance in the dog heart is illustrated during initial normocalcemia and subsequent hypercalcemia by calcium infusion. In the right panel, left ventricular performance is illustrated during initial hypocalcemia and subsequent normocalcemia by calcium infusion. Although the increases in mean peak LV *dP/dt* in the two panels are similar, in the right panel the increase in mean stroke work at a given end-diastolic pressure (10 mm Hg) is 19 g·m, about five times that observed in the left panel. For this reason, we emphasize the clinical utility of the in vivo relation between [Ca^{2+}] and cardiac pumping action, which is shown as cardiac output or work over a wide range of end-diastolic pressures in Figures 4 and 5.

It is now clear that both the heart (30,53) and the peripheral blood vessels (30,60,150) contribute to the hemodynamic response to hypocalcemia and hypercalcemia, as demonstrated when either one of these major determinants of hemodynamic performance does not change (60,150) or is held constant (53). With an intact circulation, if calcium administration enhances cardiac output, the instantaneous peripheral vascular response to calcium may not become apparent (60,149). In contrast, if cardiac output does not change, calcium administration produces increased peripheral resistance (60). These considerations are crucial in the understanding of the apparent controversy of the hemodynamic effects of hypercalcemia and hypocalcemia.

Hypercalcemia

In the operating room, acute hypercalcemia can be observed in patients with hyperparathyroidism (73) and with the intravenous injection of calcium (60,78). The latter form of acute hypercalcemia is the subject of discussion here.

Calcium ion kinetics with calcium bolus injection. The clinically reported and recommended doses of calcium chloride bolus injection, expressed in terms of mg of the calcium chloride salt rather than in terms of elemental calcium, vary from 3 to 15 mg·kg^{-1} of body weight (35,47,54,60,78,84), a very wide range. In adults, the intravenous administration of $CaCl_2$ in doses of 5–7 mg·kg^{-1} increases [Ca^{2+}] 0.1–0.2 mM, followed within 3–15 min by a decrease towards but not to baseline levels (8,47,78). That the [Ca^{2+}] increase after calcium injection is short-lived has important clinical implications, especially because of a rapid [Ca^{2+}] exchange at the contractile cell membrane (95,96,151), cardiac and hemodynamic responses are short-lived, as shown experimentally (149) and clinically (47,78). With a dose of 15 mg·kg^{-1} calcium chloride, the peak increase in [Ca^{2+}] 2 min after injection is 0.7 mM, but this is followed by a decline within minutes (60), as seen in the left panel of Figure 6.

The rate of increase and decrease in plasma [Ca^{2+}] depends on several factors. First among these is the

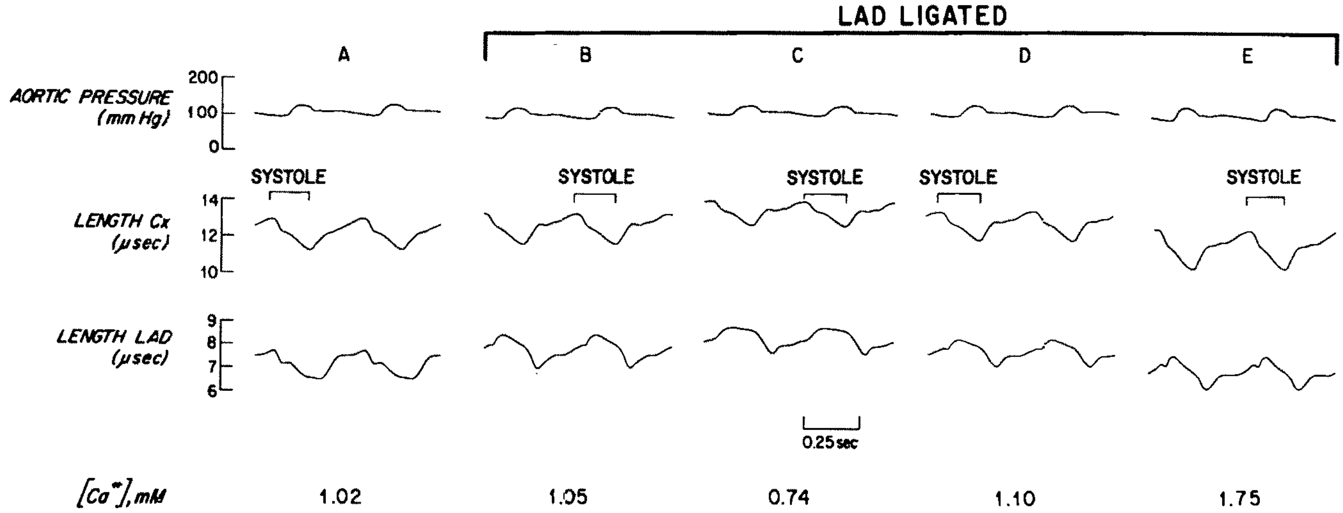

Figure 7. Regional segment length tracings obtained in the ejecting dog heart at constant mean arterial pressure (103 mm Hg), heart rate (153 beats/min), and cardiac output (3200 ml·min^{-1}). Tracings in ischemic zones are shown at different [Ca^{2+}] levels. Note that with ischemia in LAD (*B*) systolic lengthening has replaced shortening seen during the preceding control period (*A*). With hypocalcemia, systolic lengthening is exaggerated (*C*); with hypercalcemia (*E*) it is replaced by shortening. The horizontal bars indicate systole. Abbreviations: LAD, zone supplied by left anterior descending coronary artery, C_x, zone supplied by circumflex coronary artery (control). Tracings reproduced with permission from (68).

calcium ion availability (and thus the degree of ionization of the calcium salt) in the calcium preparation used for injection, together with the total amount injected and the time over which it is given. Both calcium chloride and gluconate are 10% solutions of the respective salts in 10-ml ampuls (calcium gluceptate, a 5.5% solution in 5-ml ampuls, is no longer available). However, although calcium chloride and gluconate salts are of the same concentration (10%), the calcium content in the chloride salt is greater than in calcium gluconate because the elemental calcium content in the chloride salt is 27%, whereas that in the gluconate is 9%. In addition, calcium chloride is fully ionized in solution. Thus responses to intravenous injections of calcium chloride exceed those observed with the administration of equal volumes and administration rates of calcium gluconate (76). With the exception of a different calcium content and weakly acidifying properties of the chloride salt, the advantages of one calcium salt over another have not been documented. Quantitative comparative data on calcium chloride and gluconate are not available at the present time.

The second determinant of the increase in plasma [Ca^{2+}] after the intravenous injection of calcium salts is the initial volume of its distribution and the rate of its redistribution and uptake. Although we are not aware of calcium distribution data, we believe that in the presence of a low cardiac output state (which leads to decreased rates of distribution), low calcium doses should be used to avoid excessively high calcium levels that can lead to major disturbances in cardiac rhythm and conduction (70,98), particularly in the presence of therapeutic digitalis levels (59,104).

Cardiac effects. As shown in the left panel of Figure 5, in the nonischemic ventricle, LV function curves recorded at different levels of hypercalcemia (but within the clinical range) approximate those recorded during normocalcemia (53). Even with [Ca^{2+}] held at 1.7 mM, i.e., close to the upper limit of the clinically measured hypercalcemia range, enhancement of LV pump performance is only modest as shown by a 10% increase in stroke work at a given left ventricular end-diastolic pressure (10 mm Hg). This increase is even smaller with an intermediate degree of hypercalcemia. Patient data confirm that the changes in LV function with calcium infusion in pharmacological doses are relatively small, ranging from 10% with 5 mg·kg^{-1} (78) to 20% with 15 mg·kg^{-1} (60).

In the presence of regional ischemia (Fig. 5, right panel), plasma levels of [Ca^{2+}] of 1.7 mM improve global function, as shown by a 20% increase of stroke work at a given end-diastolic pressure (10 mm Hg) (68). Although the calcium-induced improvement in regional function of the ischemic zone is not only related to an increased calcium level itself but also to interaction between different regions (i.e., changes in LV geometry), regional mechanical function is improved with hypercalcemia in both control and ischemic regions (68). As illustrated by the tracings of Figure 7, when stroke volume, heart rate, and mean arterial pressure are kept constant, hypercalcemia is associated with a decrease in end-systolic and end-diastolic length in both control and in ischemic zones, and the systolic bulge that characterizes the segmental ischemic dysfunction is substantially less with hypercalcemia than with normocalcemia. Regional systolic shortening is increased and regional performance curves are displaced to the left and upward with hypercalcemia (68).

A disadvantage of calcium infusion is the augmented myocardial oxygen consumption without an increase in coronary arterial blood flow despite increased contractility (68). Nevertheless, the improved global and regional LV function with calcium infusion as discussed supports the use of calcium in patients with ischemic heart disease, although the limitations in extrapolating experimental data derived from animals to patients should be recognized, particularly when, with intact circulation, the effects of calcium infusion on blood pressure and heart rate may also become apparent. It is reemphasized that calcium infusion has disadvantages, but so does stimulation with other positive inotropic interventions. In deciding whether calcium should be used for stimulation of the hypodynamic heart, the anticipated magnitude of cardiac improvement (greatest when initial [Ca^{2+}] is low, as discussed below), the extracardiac effects, and the above disadvantages of calcium administration should be compared to the usefulness and limitations of other positive inotropic interventions. For example, comparative data (calcium chloride vs catecholamine) obtained in the dog under hemodynamically controlled conditions have shown that, for the same increase in LV pump performance, the isoproterenol-related increase in myocardial oxygen consumption exceeds that related to calcium by a factor of three (16).

Hypocalcemia

Although the term "hypocalcemia" is generally defined by a low total serum calcium level, severe disturbances in ionized calcium homeostasis may occur without important changes in total calcium (25,51,94). This emphasizes the utility of direct [Ca^{2+}] measurement by electrode in patients with hypocalcemia to guide calcium replacement therapy. In the operating room, hypocalcemia is common after the administration of citrated whole blood (30,31,126,162) or processed albumin solutions (82) after cessation of cardiopulmonary bypass (8,45,114). In the intensive care unit, acute ionized hypocalcemia can be observed in patients with pancreatitis (43,174), sepsis (177), during low output states (54), after x-ray studies with infusion of radiographic contrast media (13,36), and in patients who require hemodialysis (67,126).

Calcium ion kinetics with citrate infusion. When citrated blood is transfused at slow rates, changes in [Ca^{2+}] and hemodynamic function are minimal (29). However, rapid transfusions at rates of 1.5 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ or more for several minutes will produce measurable (126,162) but transient (55,162) hypocalcemia and hemodynamic disturbances (126,162), as shown in the right panel of Figure 6.

Cardiac effects. The effect of hypocalcemia on LV pump performance of the nonischemic heart is shown in the left panel of Figure 5. With a reduction of [Ca^{2+}] to 50% of normal, stroke work is severely reduced at any end-diastolic pressure; at an LV end-diastolic pressure of 10 mm Hg this reduction is approximately 55% (53).

A regionally ischemic ejecting heart seems more easily depressed by hypocalcemia than is nonischemic myocardium; whereas in the absence of ischemia, depression of function is reversible with hypocalcemic levels of approximately 50% of normal; in the presence of regional ischemia, a reversible decrease of function is possible only with [Ca^{2+}] at 70% of normal (68). The magnitude of global depression with this degree of hypocalcemia is shown by the displacement of the left ventricular function curves to the right in the right panel of Figure 5. Regional function in control and ischemic zones is severely depressed by hypocalcemia; end-systolic and end-diastolic lengths are increased; the systolic bulge in the ischemic zone is exaggerated (Fig. 7); the systolic shortening is decreased and regional function curves are displaced to the right and downward (68). Hypocalcemia also is a coronary vasodilator (53,68).

The changes in cardiac function induced by severe hypocalcemia (decreased by 30–50%) as shown experimentally (53,68) support the clinical use of calcium to treat patients with calcium infusion when myocardial ischemia and moderate or severe hypocalcemia are present; this combination may occur immediately after cessation of cardiopulmonary bypass. The use of calcium under these conditions is discussed below, but it is not accepted practice in all centers.

A striking feature of the curves shown in both panels of Figure 5 is that the modest increase of LV function produced by hypercalcemia contrasts with the profound depression of function with hypocalcemia. Such contrast still holds when using a LV end-diastolic segment length rather than LV end-diastolic pressure as a measure of end-diastolic fiber length (53). The clinical importance of this contrast is that the magnitude of changes of cardiac function to be expected after calcium infusion depends on the initial [Ca^{2+}]. The increase in stroke work at any end-diastolic pressure is much greater with calcium infusion in the presence of an initial hypocalcemia (Fig. 4, right panel) than it is in the presence of an initial normocalcemia (Fig. 4, left panel); at an LV end-diastolic pressure of 10 mm Hg, this difference is as great as a factor of five. The initial [Ca^{2+}] (or the associated contractile state) as a determinant of the cardiac response to calcium infusion was originally suggested by McLean and Hastings nearly 50 years ago (110). Consistent with these observations is that, clinically, the repeated administration of calcium results in progressively lesser responses. However, the mechanism of this progressive decrease in response is not immediately clear.

Controversial Aspects to Cardiac Responses to Hyper- and Hypocalcemia

Hypercalcemia. Several reports have appeared that question the usefulness of calcium infusion in clinical doses because of the absence of measurable cardiac benefit (34,81,82). The following comments serve to explain these observations. In one study, comparative statistics on LV function during hypocalcemia (i.e., prior to calcium therapy) and after calcium infusion are not presented (81). In another study, cardiac output and arterial blood pressure did increase one minute after calcium infusion (82), a response in accord with the short-lived effects of calcium bolus infusion (47,60,149) as illustrated for a high-dose of $CaCl_2$ infusion in patients in Figure 6. If $[Ca^{2+}]$ prior to calcium infusion is normal, changes in cardiac performance are smaller than when initial $[Ca^{2+}]$ is low (Fig. 4). A number of studies lack $[Ca^{2+}]$ measurements or a complete hemodynamic profile (34,48,81,82). Calcium effects in the presence of potent inhalation anesthetics (47), furthermore, are different than those obtained in patients during neuroleptanesthesia (60). Finally, clinical data suggest that in the presence of preexisting cardiac depression secondary to coronary artery disease, calcium infusion is associated with an increase in cardiac output; whereas in patients without cardiac disease, calcium infusion is associated with increased systemic vascular resistance (60).

Hypocalcemia. The work of Bunker et al. nearly three decades ago showed a considerable reduction of several measures of cardiac performance with citrate infusion, and the term "citrate intoxication" was introduced (31). A number of subsequent experimental (30,39,126) and clinical (39,162) studies confirmed the idea of citrate-induced hypocalcemia, with associated decrease in cardiovascular function. Although the existence of citrate intoxication has been questioned (80,82), at this time the occurrence of severe but transient hypocalcemia secondary to rapid transfusion of large blood quantities in patients is recognized as an indisputable fact (39,81,126,162).

Some investigators consider the changes in blood pressure and cardiac function attending citrated blood transfusion to be minimal and unimportant (8,81,82). To explain this view, the rate of blood transfusion, not the total amount of blood given, is the determining factor in the development of hypocalcemia, as originally suggested by Bunker (29). Also, hypocalcemia depression of cardiac function becomes more readily apparent in the presence of other depressing factors such as β-adrenergic blockade (162), ischemia (68), cardiac denervation (158), or hypovolemia prior to a citrate load (126). Whether inhalation anesthetics are also predisposing factors has not been established.

Although citrate-induced hypocalcemia at one time was considered to be milder with transfusion of blood preserved in acid phosphate dextrose (69), its hemodynamic disadvantages were shown to be comparable to those of acid citrate dextrose (55).

Calcium and Peripheral Vascular Smooth Muscle

Although the role of the calcium ion in peripheral vascular smooth muscle function has been recognized for decades (74,77), it has not been considered in early reports on calcium and hemodynamic function (30,31). The calcium ion is essential to excitation–contraction coupling in peripheral vascular smooth muscle (121, 167,170) and, therefore, the peripheral blood vessels are responsive to alterations in blood $[Ca^{2+}]$ (79,99,150,153).

Peripheral Vascular Response to Acute Hyper- and Hypocalcemia

Because increased $[Ca^{2+}]$ is associated with increased contractility of vascular smooth muscle, hypercalcemia increases resistance to flow in peripheral arterial (74,77,150), renal (37), coronary (53), and cerebral (171) vascular beds. Such response has not been established for the pulmonary vascular bed. Hypocalcemia is associated with decreased peripheral vascular resistance, which is an important determinant of hypocalcemia hypotension (30,150,153).

Two main mechanisms are proposed to account for vascular responses to alterations in $[Ca^{2+}]$. First, there is a direct effect on vascular smooth muscle tone (74,77). Strong support for this is provided by the observation that systemic vascular resistance is lowered by calcium entry blocking drugs (7,108).

Second, there is an effect mediated via the autonomic nervous system, through catecholamine release or stimulation of adrenergic receptors. Catecholamine release by calcium occurs as the calcium ion is involved in "excitation–secretion coupling," a term first coined by Douglas and Rubin (50). Hypercalcemia acts as a stimulus for the release of catecholamines from both the adrenal medulla (50) and from peripheral autonomic nerve endings (89). Recent experiments in dogs, for example, show that the calcium-induced increase in systemic vascular resistance is abolished after adrenalectomy (79). Experimental data suggest that hypercalcemia may also stimulate α- and β-adrenergic receptors. After β-blockade, a calcium-induced increase in systemic vascular resistance is more pronounced than with intact β-adrenergic activity. In contrast, with α-adrenergic blockade, hypercalcemia decreased systemic vascular resistance. With both α- and β-blockade, the hypercalcemia-induced changes in resistance were variable (169). These findings may explain the different cardiovascular responses to hypercalcemia observed under different circumstances.

Controversial Aspects to the Peripheral Vascular Response to Hyper- and Hypocalcemia

Hypercalcemia. Because hypercalcemia can increase contractility of the heart and peripheral vessels, increased arterial pressure is among the most readily recorded hemodynamic changes after calcium infusion. However, a major text contains an unreferenced statement that calcium infusion is associated with a moderate decrease in arterial blood pressure (71). We have never seen arterial blood pressure decrease with calcium infusion. Whereas some experimental (149,150) and human (60,173) studies have indicated that systemic vascular resistance increases with calcium infusion, others have shown a decrease (79,160). Clearly, as noted above, calcium can produce changes in both cardiac and peripheral vascular function. The extent to which each will become apparent depends on the initial [Ca^{2+}] or cardiac contractile state (Fig. 4) and the initial autonomic nervous system activity (79). Furthermore, attention to detail—essential when recording variables reflecting the different aspects of hemodynamic function (53,150)—is not apparent in some studies (48,81,82). Finally, the state of the adrenergic system influences the hemodynamic response to calcium as mentioned above (79,169).

Hypocalcemia. A decrease in arterial pressure was documented during hypocalcemia in patients by Bunker et al. over two decades ago (30). However, the important role of the systemic vessels in the development of hypocalcemic hypotension was, although documented, not recognized (30). These original workers stressed the hypocalcemia-related decrease in cardiac performance as evidenced by a decrease in cardiac work, but there was also a marked decrease in arterial blood pressure, in part secondary to decreased systemic vascular resistance. Because arterial blood pressure is included in the numerator of the formula to calculate cardiac work, cardiac work decreased. Thus the usefulness of cardiac work as an index of cardiac performance in the presence of arterial hypotension is limited. Furthermore, the appropriate interpretation of the roles of cardiac and peripheral vascular performance during hypocalcemic hypotension is impossible if measurements of variables denoting LV pump function are lacking (48), or if decreased circulating blood volume—the very basis for blood transfusion—and hypocalcemia are both present (39).

Calcium Therapy

In the operating room and the intensive care unit, pharmacological support of hemodynamic function includes the use of catecholamines and calcium salts. Sympathomimetic amines with very short half-lives are usually administered by continuous infusion, so that their infusion rate can be readily adjusted to the need of the individual patient to thereby maintain stable hemodynamic function. In contrast, calcium salts are usually administered as bolus injections. They are not given by continuous infusion because to do so would require the calcium electrode system to be at the bedside for frequent [Ca^{2+}] measurements because, if the calcium infusion rate is constant and cardiac output decreases for reasons unrelated to calcium therapy, dangerously high [Ca^{2+}] levels would result, leading to serious cardiac rhythm disturbances (70,98).

Indications and Dosage

Adults. Because the magnitude of citrate-induced hypocalcemia with slow blood transfusion in patients is small and short-lived, we see no justification for routine use of calcium with blood transfusion. However, when blood transfusion is both rapid and prolonged (i.e., 1.5 $ml\cdot kg^{-1}\cdot min^{-1}$ for 5 min or more), an intravenous calcium bolus may be administered. Myocardial depression with a combination of hypocalcemia and β-adrenergic blockade is more severe than with hypocalcemia alone (162); therefore, calcium therapy is also justified with citrated blood transfusion at a moderate rate in patients treated with β-blockers. The calcium dose depends on the degree of hypocalcemia; an appropriate initial bolus dose is 5–7 $mg\cdot kg^{-1}$ of calcium chloride (84), repeated within a few minutes if necessary, as documented by [Ca^{2+}] measurement.

If citrated blood is used to prime the pump oxygenator reservoir, calcium chloride (approximately 500 mg/L of priming solution) may be added to minimize the hemodynamic disturbances of hypocalcemia upon initiation of cardiopulmonary bypass (35,45,84). When citrated blood is used for priming, heparin is required for anticoagulation.

In some centers, including the Massachusetts General Hospital, calcium chloride is routinely used in patients with cardiac operations after termination of cardiopulmonary bypass (84). Appropriate bolus doses range from 7 (84) to 15 $mg \cdot kg^{-1}$ (35,60) over 30–60 sec, and are repeated if necessary (35,78). According to a recent report, on average, 2 g of calcium chloride is given after cessation of bypass in adult patients (35). We believe that monitoring [Ca^{2+}] is essential to guide appropriate calcium replacement therapy. Calcium chloride is also routinely used in patients with asystolic cardiac arrest, in a dose ranging from 5 to 12 $mg \cdot kg^{-1}$ (21,84). Although comparative data are not available, the dose of calcium gluconate (in $mg \cdot kg^{-1}$) necessary to achieve a given [Ca^{2+}] increase would be expected to be 2.5–3 times the amount of calcium chloride (71).

Infants and children. By convention, the calcium salt used in pediatric patients is calcium gluconate, primarily because it is considered a safer calcium preparation than calcium chloride; safer in terms of incidence of cardiac arrhythmias. However, the safety of a given calcium preparation depends on the total amount of calcium given and on the time period over which it was administered, on the bioavailability of the calcium ion in the selected calcium preparation, and on the volume of initial distribution. All these factors determine the rate of increase in [Ca^{2+}] in the calcium recipient, and it is this rate of change of [Ca^{2+}] together with the absolute [Ca^{2+}] levels that determine the occurrence of cardiac rhythm or conduction disturbances. A second reason for use of calcium gluconate in pediatrics is that it is said to disturb the acid–base balance less than does calcium chloride, but this is not a problem with short-term calcium replacement therapy.

Calcium replacement is indicated during extensive pediatric surgery with major blood loss, when blood loss and replacement should be measured in terms of estimated circulating blood volume. The dose of calcium gluconate is approximately 100 mg for each 100 ml blood transfused, but frequent [Ca^{2+}] measurements are necessary, as hypocalcemia still can develop despite calcium therapy at this rate (46). Thus the dose and appropriate timing of calcium administration necessary to eliminate a severe hypocalcemia still needs definition.

Calcium is also indicated with exchange transfusion in newborns (66,134). Although the recommended dosage is reported as 100 mg of calcium gluconate for each 100–150 ml of blood exchanged, this dose may not be sufficient to prevent hypocalcemia (66). Therefore, close [Ca^{2+}] monitoring is again essential. In neonatal hypocalcemia, calcium gluconate is recommended (200 $mg \cdot kg^{-1}$) only for the treatment of overt tetany or seizures due to severely depressed [Ca^{2+}] levels (26,27). For cardiac arrest in children, calcium gluconate (10 $mg \cdot kg^{-1}$) is recommended (161).

Complications of Calcium Infusion

A most dramatic description of the adverse hemodynamic effects that can occur with calcium infusion was presented nearly sixty years ago (101). The author of this report received a bolus injection of calcium chloride and experienced dizziness, syncope, and respiratory failure. Extensive details are not available, but the electrocardiogram showed sinoatrial block and marked bradycardia. Cardiac massage through the abdominal wall at the costal margin was required to revive this volunteer.

Even if hypocalcemia is documented, calcium administration in pharmacological doses can lead to major disturbances of cardiac rhythm including sinus arrhythmia, bradycardia, A–V dissociation, and junctional rhythm (33). The potential risk of calcium bolus injection in patients treated with digitalis has been alluded to above (104).

A complication of calcium administration that is not life-threatening but noteworthy is the irritation of vessel walls and the necrosis of subcutaneous tissue upon infiltration of intravenous solution carrying calcium chloride or gluconate (17,175,179). Thus calcium should be infused into a (preferably large) vessel with established patency. Whether calcium can be safely infused into the aorta for treatment of neonatal hypocalcemia is a matter of controversy (17,175).

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Clinical Reports

Acute Abstinence Syndrome after Epidural Injection of Butorphanol

Steven J. Weintraub, MD, and J. Stephen Naulty, MD

The abstinence syndrome in humans can be produced by the systemic administration of narcotic antagonists to patients who are physiologically dependent upon narcotics (1). Because of their unique receptor interactions, drugs in the category of narcotic agonist–antagonists have the potential for the precipitation of acute symptoms of narcotic withdrawal. We present here a case report of the acute abstinence syndrome precipitated by an epidural injection of the narcotic agonist–antagonist butorphanol in a term parturient after cesarean delivery.

Case Report

A 37-year-old gravida 6, para 2, woman presented for elective repeat cesarean delivery at term. Fetal presentation was breech. Her first cesarean delivery was performed seven years earlier under epidural anesthesia without difficulty.

Her past medical history revealed longstanding, mild, rheumatoid arthritis for which she received occasional antiinflammatory medications, none during this gestation. She had a history of alcohol abuse, but denied any alcohol consumption for over one year. She had received general anesthesia for open reduction and internal fixation of a right wrist fracture three years earlier. She also received general anesthesia for a tonsillectomy in childhood. She had a 20-pack/year history of smoking. Besides prenatal vitamins, she stated that she took no other medications at home, including narcotic analgesics.

She weighed 57 kg, was 170 cm tall, her blood pressure was 110/70 torr, and her pulse was 72 and regular. The remainder of her physical examination was unremarkable.

On the morning of surgery, a lumbar epidural catheter was inserted at the second lumbar interspace through which the patient received 28 ml of 2% lidocaine with 1/200,000 epinephrine in divided doses, with a resulting level of sensory anesthesia to the first thoracic dermatome.

After an unremarkable delivery of a normal female infant, with Apgar score 8/9, the patient received an epidural injection of 2 mg of butorphanol dissolved in preservative-free normal saline to a total volume of 10 ml as part of an approved research protocol investigating the use of extradural butorphanol for post-cesarean delivery analgesia.

Approximately 5 min after the injection, the patient became acutely restless and agitated. Sensory anesthesia to the second thoracic dermatome was present. She became flushed and was noted to be yawning and producing copious tears. She complained of nausea and retched for 1–2 min. Her blood pressure decreased from a preinjection level of 115/70 to 80/50 torr. She developed a sinus tachycardia with a pulse of 130. She was treated with 15 mg of ephedrine intravenously, supplemental oxygen by face mask, Trendelenburg position, and a rapid infusion of 500 ml of Ringer's lactate solution. Her hypotension and tachycardia rapidly resolved, but she remained restless and agitated during the remaining 15 min of the surgical procedure. She was brought to the recovery room, where her pulse and blood pressure remained normal. Her agitation resolved slowly over 1 hr without further therapy.

After the procedure, the obstetrician volunteered the "confidential" information that the patient had been taking oxycodone (Percodan) every day for at least a year prior to delivery. With this information,

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Address correspondence to Dr. Weintraub, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

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it became apparent that the patient's symptoms were those of the acute abstinence syndrome precipitated by the epidural injection of the narcotic agonist–antagonist butorphanol.

Four hours and fifteen minutes after initiation of her epidural anesthesia and one hour after disappearance of the anesthesia, the patient received hydromorphone, 1 mg intramuscularly, for relief of incisional pain. Over the next 24 hr, the patient received an additional 2 mg of hydromorphone intramuscularly and nine tablets of oxycodone orally for relief of pain. She received no other medications.

Discussion

The administration of butorphanol as an epidural injection is a safe and effective means of providing postoperative analgesia (2). The mechanism of action appears to be related to the ability of butorphanol to bind with central nervous system opiate receptors after diffusion from the epidural space into the neuraxis (3).

Small amounts of drugs injected into the epidural space are absorbed into the systemic circulation, resulting in detectable serum levels. Systemic absorption of butorphanol from the highly vascular epidural space of the term parturient may explain the timing of the acute abstinence syndrome in our patient. Blood levels of meperidine after epidural injection have resulted in detectable serum levels as early as 5 min after injection (4). Similarly rapid vascular uptake has been demonstrated for an epidural injection of morphine sulfate (5).

Our patient exhibited both cerebral (systemic) and spinal (local) effects of the epidural injection of butorphanol. The cerebral effect was seen as the acute abstinence syndrome, while the spinal effect was seen as the production of postoperative analgesia. The analgesia can be inferred from the patient's markedly decreased requirement for parenteral narcotics in the first 24 hr postoperatively compared to controls, as well as the fact that her epidural anesthesia had worn off for almost 1 hr prior to her request for analgesics in the recovery room (2).

One reference exists to hypotension, tachycardia, and flushing precipitated by the epidural injection of buprenorphine in two morphine-addicted patients with chronic pain (6). However, the authors did not correctly attribute the observed signs and symptoms to an acute abstinence syndrome, but rather to an idiosyncratic response to buprenorphine.

The infant in our case was not exposed to butorphanol because injection was made after delivery and clamping of the umbilical cord. She weighed 3685 g and had Apgar scores of 8/9. She was described as an excessively irritable infant during her first 48 hr of life, but did not require any therapeutic intervention in the nursery.

With the increasing use of extradural narcotics for relief of chronic and postoperative pain and with new research into the use of extradural narcotic agonist–antagonists, there exists the potential for complex cerebral and spinal opiate receptor interactions. An exhaustive medication history is essential to avoid administration of narcotic agonist–antagonists to patients addicted to narcotics.

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Comparison of Lumbar and Thoracic Epidural Morphine for Relief of Postthoracotomy Pain

Glenn A. Fromme, MD, Lester J. Steidl, MD, and David R. Danielson, MD

The use of epidural narcotics has revolutionized postoperative analgesia. Narcotics injected in this fashion provide excellent analgesia with a relatively low incidence of side effects. In addition a significant improvement in postoperative pulmonary function has been demonstrated with epidural narcotics as compared to narcotics given intravenously (1). Patients having operations that are known to cause significant impairment in postoperative pulmonary function stand to benefit a great deal from improved postoperative analgesia, especially those with preexisting pulmonary disease. Early reports stress the segmental nature of analgesia with epidural morphine and suggest placement of the epidural catheter at the dermatome level corresponding to the origin of the pain.

We, therefore, adopted the practice of placing thoracic epidural catheters in patients undergoing thoracotomy. Unfortunately, this requires placement of epidural catheters at the T5–6 level for patients undergoing standard thoracotomy incisions, a level at which interspaces are most narrow and spinous processes are most angulated. In addition, the potential for spinal cord trauma always exists whenever needles are inserted above L2. Therefore, in patients in whom insertion of a thoracic epidural catheter was not possible technically, we began to place lumbar epidural catheters. Because of earlier reports of segmental distribution of analgesia with epidural narcotics, our initial expectations were that patients with lumbar epidural catheters might not achieve adequate analgesia or would only achieve adequate analgesia with higher doses. Surprisingly, we noted that with similar doses, the analgesic effect of lumbar epidural morphine was similar to that of patients receiving thoracic epidural morphine.

We, therefore, decided to study retrospectively a group of patients who had undergone thoractomies with postoperative analgesia provided by either thoracic or lumbar epidural morphine. Our objectives in this study were to evaluate the efficacy of morphine administered in the lumbar epidural space in relieving postthoracotomy pain and to compare this to analgesia provided by thoracic epidural morphine.

Methods

We reviewed the charts of 122 patients requiring analgesia for postthoracotomy pain. Group I ($n = 30$) received lumbar epidural catheters and group II ($n = 92$) received thoracic epidural catheters. There was no significant difference between the two groups with respect to age, height, and weight. All patients received inhalation anesthetics and intravenous narcotics during surgery. Epidural catheters were inserted either prior to surgery or immediately postoperatively in the recovery room. We used a midline approach primarily, although in a few instances a paraspinous approach was used. Initial epidural morphine injections were administered in the recovery room when patients first complained of pain. Initial dosage was estimated based on patient's age, physical status, size, and degree of chronic pulmonary disease. The low range of this estimate was administered, and additional 1-mg increments were titrated until adequate analgesia was achieved. Our initial starting dose in the thoracic group was 3–4 mg. In the lumbar group, because we initially anticipated that patients would require at least the same dosage if not larger, our initial injection was 5–6 mg. Patients were instructed to ask for additional epidural injections as soon as their pain began to return. Repeat epidural injections were available on a 24-hr basis upon request as were intravenous or intramuscular narcotics if pain was not relieved with epidural morphine within 1 hr of injection. All patients were monitored in an ICU for at least 12 hr after the last epidural injection.

The mean value for the dose of morphine, total

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Address correspondence to Dr. Fromme, Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905.

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volume of injectate, and duration of analgesia per injection were calculated for each group, and the number of patients who requested additional analgesics while receiving epidural morphine was recorded.

Results

The efficacy of epidural morphine in providing post-thoracotomy analgesia was determined by comparing the number of patients who requested additional analgesics while receiving epidural morphine in each group. Only 2 out of 30 patients (6.7%) were not satisfied with the analgesia produced by lumbar epidural morphine. This did not differ statistically from the 5 of 92 patients (5.5%) requesting additional analgesics while receiving thoracic epidural morphine. Dosage, volume, and duration of analgesia data are shown in Table 1.

Discussion

This study was prompted by the finding that patients in whom lumbar epidural catheters were placed (after failed attempts to place thoracic epidural catheters) received clinically indistinguishable analgesia from the group that had been treated with thoracic epidural morphine. Bromage has suggested that lipid solubility plays a role in determining the degree of spread of spinally administered narcotics (2). Highly lipid soluble narcotics such as fentanyl readily and rapidly bind to opiate receptors with little spread throughout the CSF. Poorly lipid-soluble agents, such as morphine, bind less readily with opiate receptors and thus migrate to a greater degree throughout the CSF. The lack of statistically significant differences in dosage and volume in our two groups of patients suggests extensive CSF spread with morphine.

This property of morphine can be thought of as both an advantage and a disadvantage for spinal administration. An advantage, because it allows patients with upper abdominal and thoracic incisions to have catheters placed at a safer and technically easier level and still receive superior analgesia. The disadvantage is that this extensive diffusion could allow significant levels of morphine to diffuse centrally and result in respiratory depression. Indeed, although the literature contains numerous reports of respiratory depression associated with epidural morphine, we know of none with epidural fentanyl and only one with epidural methadone (3). One would think that if injections at L3–4 or T5–6 require the same dosage and volume, while producing the same quality and duration of analgesia, the distribution within the CSF must be the same. This implies that relatively even distribution throughout all CSF occurs before binding is complete and suggests that respiratory depression may not be a function of CSF levels in the brain, but may be more related to patient sensitivity. In our series the incidence of respiratory depression has been less than 2%. Those patients who have experienced severe respiratory depression with epidural morphine have been elderly, debilitated, or have had severe obstructive pulmonary disease, all of which are known to make people more susceptible to narcotic side effects (4).

Table 1. Dosage, Volume of Injectate, and Duration of Analgesia with Lumbar and Thoracic Epidural Morphine

	Lumbar (*n* = 30)	Thoracic (*n* = 92)	Difference
Dosage (mg)	6.2 ± 1.3	6.3 ± 1.3	NS[a]
Volume (ml)	12.2 ± 2.6	13.0 ± 2.1	NS[a]
Duration of analgesia (hr)	10.9 ± 3.5	12.1 ± 4.3	NS[b]

[a] No significant difference (χ^2 analysis, Yate's correction).
[b] No significant difference (Wilcoxan rank sum test).

In conclusion, lumbar epidural morphine provides postoperative analgesia after thoracotomy that is clinically indistinguishable from that provided by thoracic epidural morphine with respect to dosage, duration, and quality of analgesia.

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Letters to the Editor

Epidural Buprenorphine for Postoperative Pain Relief

To the Editor:

We would like to comment on the recent article by Lanz et al. (Anesth Analg 1984;63:593–8) on the use of epidural buprenorphine for pain relief after major orthopedic surgery. Over the last few years we have gained considerable experience with the use of buprenorphine administered into the epidural space and we have found our results to be somewhat at variance with those of Lanz and his associates.

It is our contention that the benefits of epidural and intradural (subarachnoid) opiate administration accrue from the high quality of analgesia provided at very low dosage. It seems, therefore, unnecessary and illogical to use the same dosage of opiate in the epidural space as for intramuscular or intravenous injection. We have used a dosage of 60 μg (0.06 mg) of epidural buprenorphine diluted to 10 ml with physiological saline and compared this with the analgesic efficacy of intramuscular morphine (0.15 mg/kg) and epidural morphine (2 mg diluted to 10 ml) in patients after major hip, major spinal, and major abdominal surgery (1–3). Our results indicate that 60 μg of epidural buprenorphine repeated when necessary (rarely more frequently than every 8 hr) provides consistent and satisfactory analgesia when using this technique as the sole means of postoperative analgesia. Lanz et al. found that patients receiving 0.15 mg of epidural buprenorphine had less pain than their control group, and those given 0.3 mg of buprenorphine fared best of all. Surely it comes as no surprise that those given opiates for postoperative pain suffered less pain than those given nothing. This does not prove that *epidural* buprenorphine works. To prove that spinal opiates work by a local (spinal) effect it is necessary to show that analgesia thus provided is done so at a dosage that would be insufficient when given by the usual parenteral routes. It is similarly not surprising to learn that a dosage of 0.3 mg has a longer duration of action than half that dosage. Elementary pharmacokinetic principles of drugs following first order kinetics provide the answer to this effect. A rational response to such an effect would be to "top-up" the epidural as necessary.

The authors noted that $Paco_2$ values in control patients and in those receiving epidural buprenorphine remained within the normal range. They then noted that "$Paco_2$ levels after 0.3 mg buprenorphine epidurally were slightly but significantly greater ($P < 0.05$)." There follows in the discussion section of their paper a full paragraph on the possible explanation of this statistical fact. If $Paco_2$ values remained within a normal range surely it is sufficient to document this fact. Statistically significant differences within a normal range of results have no meaning in a clinical setting.

There have been many studies (4–8) using highly sensitive methods of assessing respiratory effects of epidural opiates (e.g., CO_2 response curves and measurement of mouth occlusion pressures) and all have shown that some loss of CO_2 sensitivity occurs. We believe that this merely demonstrates that opiate administration by any route, including epidural and intradural (subarachnoid), will be followed by respiratory depression, if a method of assessment is sufficiently sensitive to detect it. Opiates cause respiratory depression. What is important is whether or not this is clinically significant. Lanz et al. have shown in their paper that it is not. We have similarly documented this fact (4).

Finally, the authors make an unsubstantiated statement that "the effective epidural and intravenous doses of buprenorphine do not differ." This is not so. There is to date in the literature no scientific comparison of the potencies of epidural and intravenous buprenorphine. In an ongoing study, we are presently comparing the use of epidural buprenorphine with intravenous buprenorphine for pain relief in patients after thoracotomy. Our results to date indicate that significantly more buprenorphine is required by patients receiving the drug intravenously. Furthermore, we are measuring plasma levels of buprenorphine after its administration by either route and we have found significantly smaller plasma levels after epidural administration. These studies are reaching completion and shortly will be ready for publication.

D. F. Murphy, MB, BCh, BAO, FFARCSI
J. Cahill, MB, BCh, BAO, FFARCSI
G. Fitzpatrick, MB, BCh, BAO
M. MacEvilly, MB, BCh, BAO, FFARCSI
Anaesthetic Unit
Dr. Steeven's Hospital
Steeven's Lane
Dublin 8
Ireland

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In Response:

We thank Dr. Murphy et al. for their interest in our study on epidural buprenorphine.

It seems to us an incorrect generalization that very low epidural doses of (all) opiates provide high quality of anesthesia and that, therefore, lower epidural than systemic doses of opiates are required, even when administered as a single-shot technique. De Castro and Lecron (1) report the ratio between clinically common intravenous single injection doses and epidural single injection doses to be 10:1 for meperidine; 2–3:1 for morphine, nicomorphine, methadone, diamorphine, and hydromorphine; and 1:1 for phenoperidine, fentanyl, lofentanyl, and buprenorphine. These relationships have not been changed by more recent investigations. The differences between the drugs may be explained partly by different physicochemical properties and, therefore, different pharmacokinetics (1). Precise, controlled comparisons of dose–effect relationships between epidural and systemic administration are lacking for most opiates, including buprenorphine.

The observation that a single injection epidural dose of 0.06 mg of buprenorphine provides consistent and satisfactory analgesia for 8 and more hr is in contrast to our results and those of other authors. After comparable surgery, 40–70% of our patients who had received 0.15 mg of buprenorphine complained of moderate to very severe pain within the first 8 postoperative hr; 10–40% of the patients who had received 0.3 mg of buprenorphine complained of moderate to very severe pain during the same period. The increase in dose of buprenorphine from 0.15 to 0.3 mg markedly intensified the postoperative analgesia for up to 12 hr. After the disappointing analgesia from the 0.1-mg buprenorphine dose used in our pilot study, we decided to administer 0.15 and 0.3 mg. Most probably, other authors (2–6) also chose these dosages after having similar experiences. After abdominal surgery, daily epidural doses of up to 0.75 mg were required until the second postoperative day (3). Even the intrathecal administration of 0.15 mg of buprenorphine resulted in satisfactory analgesia for only 8 hr after surgery (7). Due to these results, we and the above authors came to the conclusion that in order to achieve analgesia of satisfactory intensity and duration, single injections of buprenorphine into the epidural space should be in doses in the range of systemic doses.

That the analgesia produced by epidural buprenorphine is due to the effect of the narcotic on the spinal cord, not on the brain, is indicated by the fact that the duration of postoperative analgesia is greater with 0.3 mg of epidural buprenorphine than it is with a similar intramuscular dose.

With the observation that 0.3 mg of buprenorphine epidurally resulted in more intensive, more reliable, and longer lasting postoperative analgesia than did 0.15 mg of buprenorphine, we did not intend to confirm a known pharmacokinetic principle; our intent was to define the magnitude of changes in postoperative analgesia when the dose of a single injection of epidural buprenorphine was increased from 0.15 to 0.3 mg.

About changes in Pco_2: statistically significant increases in Paco_2 due to buprenorphine within the physiological range indicate a pharmacological effect. Under certain circumstances, such changes may result in Pco_2 levels outside the normal physiological range. Therefore discussing such effects may be of clinical interest and significance.

Egon Lanz, MD
Dieter Theiss, MD
Institut für Anaesthesiologie
Universitätsklinik Mainz
Langenbeckstr. 1
6500 Mainz 1
West Germany

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A Substitute for 4% Cocaine

To the Editor:

Gross et al. (1) report that topical lidocaine 3% in 0.25% phenylephrine is "as effective as cocaine" for blind nasotracheal intubation. The combination of lidocaine and phenylephrine as a suitable substitute for cocaine before blind nasotracheal intubation is, however, not new and was previously described by Jacoby in this journal in 1970 (2).

Jacoby states in this article: "A satisfactory substitute for cocaine consists of 3 parts of 4% lidocaine mixed with 1 part of 1% neosynephrine nasal medication. The resulting mixture contains 3% lidocaine and 0.25% neosynephrine and performs the same functions as cocaine, but doesn't require narcotic precautions (2)." Furthermore, Jacoby has utilized this combination for over 30 yr, and continues to believe it to be an excellent solution.

Michael E. Goldberg, MD
Jay J. Jacoby, MD, PhD
Thomas Jefferson University
Jefferson Medical College
Philadelphia, PA 19107

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Epidural Blood Patch in Outpatients: A Simpler Approach

To the Editor:

The report by Ravindran (1) of 20 epidural autologous blood patches (EABP) performed on an outpatient basis, prompts me to share my personal experiences in this area. Having performed approximately 60–70 EABPs on outpatients, I would agree that this is a relatively simple procedure that does not usually merit overnight hospital admission. However, I have found that starting an electrolyte infusion before the procedure and encouraging the patient to drink large quantities of fluid afterward, as described in this report, are unnecessary. I perform the EABP in the emergency room with the patient in either the lateral or sitting position. Not infrequently, dural tap is a complication of a difficult epidural, and I therefore usually select the approach that is most likely to result in successful location of the epidural space. After injection of 10 ml of blood, the patient rests quietly for 1 hr, after which he or she is discharged and contacted the next day by telephone for followup. With this simple protocol only one patient did not have total relief of headache and related symptoms. Because a more invasive approach (e.g., intravenous infusion of 2 L of fluid) is costly and incurs the risk of complications, albeit minor ones, it should not be advocated without evidence that it improves outcome. Finally, I have found that overzealous "pushing of oral fluids" to increase CSF production results in little improvement of symptoms, while necessitating multiple, uncomfortable expeditions to urinate!

Sheila E. Cohen, MB, FFARCS
Department of Anesthesia, S-272
Stanford University School of Medicine
Stanford, CA 94305

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Pressurized Infusion System

To the Editor:

Drs. Philip and Philip (1) are to be congratulated for having improved upon a massive transfusion device we previously described (2) by making it possible to pressurize four bags (1) instead of two (2). Their clinical observations (1) agree with ours (2) with regard to the ease of such a system, which can be operated by only one person without fear of massive air embolism; the fact the system allows almost continuous fluid administration if Y-solution administration sets are used; and the large amounts of fluid that can be rapidly infused (300–500 ml/min) (1). We added to our system a low resistance blood warmer to decrease the incidence of hypothermia and the viscosity of the blood. This may further speed up the rate of infusion (2).

Luc Quintin, PhD, MD*
Department of Anesthesiology
Hopital Cardiologique
69394 Lyon
France

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Isoflurane and Hepatic Dysfunction

To the Editor:

The recent clinical report of repeated isoflurane anesthesia in a patient with hepatic dysfunction by McLaughlin and Eger (1) is interesting. They attribute hepatic dysfunction after an isoflurane anesthetic to ascending cholangitis and passage of a gallstone. The diagnosis is based on an ultrasound examination, confirmed by computerized tomography, which revealed a dilated biliary tree indicative of a distal common bile duct obstruction. The authors report transaminase, phosphatase, and bilirubin levels before and after three consecutive isoflurane anesthetics. They conclude that, "the decrease in transaminases after the second and third administration of isoflurane is not consistent with anesthetic induced hepatitis." However, their data clearly show that the GGTP and alkaline phosphatase levels peaked 11 days after the first isoflurane anesthetic and 11–15 days after the second and third isoflurane anesthetics. This is shown graphically in Figure 1. The smaller peak after the second and third anesthetics may reflect the lower concentrations of isoflurane used during these procedures. The data do not support the authors' conclusions that (a) "hepatic injury after anesthesia with halogenated anesthetics

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*Current address, Neuropharmacology Group, Roussel, 93230 Romainville, France.

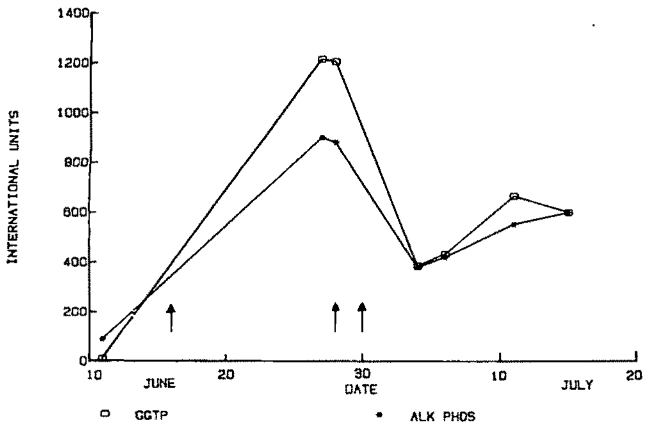

Figure 1. Graphic presentation of GGTP and alkaline phosphatase (ALK PHOS) levels reported by McLaughlin and Eger (1). The arrows indicate administration of isoflurane anesthesia.

is not necessarily a consequence of that anesthetic, even in the absence of other immediately obvious causes," and (b) "repeated anesthesia with a halogenated agent in the presence of preexisting hepatic injury does not necessarily increase that injury." The authors suggest in their article that enflurane and isoflurane probably do not cause liver injury. However, evidence is mounting that enflurane, on rare occasions, may cause hepatotoxicity (2). Finally, the data presented by McLaughlin and Eger do not convincingly show that isoflurane was not the cause of hepatic damage in their patient.

Donald H. Lambert, PhD, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis St.
Boston, MA 02115

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In Response:

The increases in alkaline phosphatase and GGTP emphasized by Dr. Lambert should not be construed as being indicative of injury to hepatocytes. Widmann (1) uses the following criteria: "The enzyme most often measured to indicate bile duct obstruction is *alkaline phosphatase* (ALP)." "Obstruction of extrahepatic bile ducts causes up to tenfold elevations [of alkaline phosphatase], even if obstruction is incomplete. Hepatocellular disease often causes modest elevations of ALP. Elevated GGT [gamma glutamyl transpeptidase] correlates better with obstruction and cholestasis than with pure hepatocellular damage, and GGT is considered one of the 'obstructive' enzymes." Thus, the marked increases in these enzymes in our patient combined with the modest (after the first isoflurane anesthesia) or minimal (after the second and third isoflurane anesthesias) increases in SGOT and SGPT indicate cholestasis or obstruction rather than injury to liver cells. This diagnosis was supported by the ultrasound examination, which revealed a "dilated biliary tree indicative of a distal common bile duct obstruction." As noted in our report, the observations made by ultrasound examination were confirmed by computerized tomography.

If isoflurane is responsible for the changes found in this case, it must cause distal common bile duct obstruction by some as yet unknown mechanism. Such a disease entity would be much different from that proposed by Lewis et al. for enflurane (2). These investigators suggest that enflurane (and halothane) cause hepatocellular necrosis.

Another aspect of this case did not fit the diagnosis of "enflurane hepatitis." Injury after the second or third exposure is supposedly greater than after the first exposure. In our case, the enzymes indicating hepatocellular injury *decreased* after the second and third exposure. This does not seem consistent with an "allergic" response to isoflurane. Similarly, the absence of atopy, rash, or eosinophilia does not indicate an allergic response.

Dr. Lambert calls our attention to the enzymes indicative of cholestasis or obstruction, alkaline phosphatase, and GGTP. He notes that these increased after the second and third isoflurane administrations, and that the increases were smaller than after the first administration. He suggests that "the smaller peak after the second and third anesthetics may reflect the lower concentrations of isoflurane used during these procedures." However, the "dose" of isoflurane (i.e., the MAC-hr of isoflurane administration) was greater for the combined second and third administrations than for the first administration. The dose was greater because the duration of exposure to isoflurane for the second and third anesthetics (230 min) was longer than after the first anesthetic (65 min), and the concentrations were not dissimilar (i.e., 0.5–1.5% for the first anesthetic and 0.25–1% for the second and third anesthetics).

Dr. Lambert also comments that "evidence is mounting that enflurane, on rare occasions, may cause hepatotoxicity" and cites the article by Lewis et al. We disagree regarding the evidence and its relevance. First, lessons learned from enflurane may or may not apply to isoflurane. Second, the evidence given by Lewis et al. is not "mounting" in the sense that the incidence is increasing. The incidence of reports of hepatic injury after enflurane anesthesia relative to the use of enflurane has remained constant (EI Eger, unpublished data). Third, the evidence given by Lewis et al. is flawed (EI Eger, unpublished data). For example, these investigators included a case in which injury did not appear for 31 days after anesthesia. A second example is the inclusion of a case in which injury appeared about three weeks after anesthesia and was associated with cardiogenic shock.

Finally, we did not suggest that "enflurane and isoflurane probably do not cause liver injury." We did suggest that injury would be less likely with these agents than with halothane or chloroform. We also wrote that "under conditions of prior enzyme induction and severe hypoxia, all anesthetics—inhaled and injected—can cause hepatic dysfunction . . ." We were careful to indicate that one cannot prove that an anesthetic does not cause injury to the liver.

However, whether isoflurane does or does not cause hepatic injury was not the point of our article. Rather, we hoped to demonstrate that "hepatic injury after anesthesia with a halogenated anesthetic is not necessarily a consequence of that anesthetic . . . [and that] . . . repeated anesthesia with a halogenated agent in the presence of preexisting hepatic injury does not necessarily increase that injury." We continue to believe that our case illustrates these two points.

Desmond F. McLaughlin, MD
Surgery Division
Lutheran General Hospital
Park Ridge, IL 60068

Edmond I. Eger II, MD
Department of Anesthesia
University of California
San Francisco, CA 94143

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Guide Wire Complication during Central Vein Catheterization

To the Editor:

The modified Seldinger technique with the use of a guide wire for central vein catheterizations (CVC) is very frequently used in critical care. Complications derived from the use of the guide wire are rare.

We report a complication while using a guide wire during the insertion of a right subclavian catheter for Swan–Ganz placement. Standard guidelines for percutaneous catheterization using the "over the wire" technique were followed (1,2). The vessel was entered, then a spring guide wire was advanced into the vein through the needle. After entering approximately 10 cm, resistance to further progression or withdrawal was noticed and the patient experienced some discomfort; the needle was withdrawn. Chest x-rays were taken and a coil or knot of the guide wire in the territory of the right subclavian vessels was observed.

Because similar manipulations to unknot other types of catheters have been reported (3,4), an 8-gauge French Teflon vessel dilator was advanced over the guide wire while applying gentle traction to the proximal end of the same. This maneuver resulted in complete extraction, without any apparent complications in the followup.

The use of a guide wire for CVC is considered to be safe and easy; however, occasionally complications are encountered (5). Some of the complications can be prevented through familiarity with the procedure and its materials. If the cannula is properly placed into the vessel, the guide wire should advance smoothly. To avoid fragmentations of the wire, plastic cannulas over the needles are preferred for CVC. If during guide wire removal any resistance occurs, chest x-rays should be taken to clarify its position and any possible kinking, knotting, coiling, or fragmentation. Careful guide wire inspection upon removal to ascertain that no fragments have been left inside the patient is recommended.

Luis Teba, MD
Mostafa Zakaria, MD
Franklin Schiebel, MD
Department of Anesthesiology
West Virginia University Medical Center
Morgantown, WV 26506

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Anesthetics and Theophylline Metabolism

To the Editor:

I was interested in the paper by Berger et al. (1) because in our work it has been necessary to identify an anesthetic protocol that allows relatively unhindered elimination of theophylline in dogs. Unfortunately, some of the conclusions made by these workers may be incorrect with respect to the lack of effect of halothane and enflurane on the rate of theophylline elimination.

In similar studies (Table 1) we have found that halothane and enflurane had a statistically significant inhibitory effect on theophylline elimination in mongrel dogs. The theophylline half-lives in our studies were 3.3 times control when the dogs received halothane and 1.6 times control in the case of enflurane. Although there were differences between the preparation protocols of Berger et al. (1) and ours, none stand out as being responsible for the differing results; for example, our dogs did not receive succinylcholine and breathed oxygen instead of air. On the other hand, there was a major discrepancy in the length of the experiments (32 min vs 300 min used by us), which may account for the differing conclusions. The elimination half-lives reported by Berger et al. (1) were calculated with heavy dependence on the 16 and 32 min values for serum theophylline concentration. This small number of points and short sampling period are not usual practice in obtaining pharmacokinetic information on drugs such as theophylline. If we recalculate some of our data using the closest time points to theirs (15 and 30 min), the apparent half-lives of serum theophylline become 105 and 90 min in the presence of halothane and chloralose, respectively. These are close to the values reported by Berger et al. (1).

Table 1. Effect of Anesthetics on Elimination of Theophylline in Dogs[a]

	Control, thiopental alone (n = 5)	Chloralose plus thiopental (n = 4)	Isoflurane plus thiopental (n = 2)	Enflurane plus thiopental (n = 5)	Halothane plus thiopental (n = 5)
k_e (min^{-1})	0.0024[b,c]	0.0020[b]	0.00098	0.0015	0.00074
	(0.0006)	(0.0009)		(0.0003)	(0.00028)
$t_{1/2}$ (min)	283	341	707	465	939

[a] Dogs were induced with thiopental (35 mg/kg) and then maintained with the anesthetic indicated or no further anesthetic in the case of controls. Theophylline (10 mg/kg) was infused in 10 min and then venous blood samples were taken every 15 min from the end of infusion except for controls from which the samples were taken every 30 min. The chloralose dose was 80 mg/kg. Halothane, enflurane, and isoflurane were administered at between 1 and 2% to provide the depth of anesthesia required for our experiments. Serum theophylline concentrations were determined by high performance liquid chromatography (5). Values are reported as means ± standard deviation. Statistical significance was evaluated by analysis of variance combined with Newman-Keuls test.

[b] $P < 0.01$ as compared to halothane plus thiopental.

[c] $P < 0.005$ as compared to enflurane plus thiopental.

In conclusion, halothane strongly inhibits theophylline elimination in the dog and enflurane inhibits to a lesser extent. Because halothane is metabolized to a greater extent by the mixed function oxidases of the liver than is enflurane, these observations are consistent with these anesthetics inhibiting theophylline elimination by acting as competitive substrates (2–4). The possibility of a clinically significant interaction between theophylline and halothane remains open.

Kanji Nakatsu, PhD
Associate Professor
Department of Pharmacology and Toxicology
Queen's University
Kingston, Ontario, Canada
K7L 3N6

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5. Nakatsu K, Owen JA, Scully K. Reliable fifteen-minute assay for theophylline. Clin Biochem 1978;11:148–9.

In Response:

We thank Dr. Nakatsu for his interest in our paper (1). His data do suggest that a longer sampling period for theophylline than that in our study might have yielded calculated elimination half-lives different than those we obtained.

Our study, however, was performed to determine whether differences in arrhythmogenicity between halothane and enflurane anesthesia after aminophylline administration could be related to differences in theophylline metabolism during the period in which arrhythmias occurred, that is, within 15 min after beginning halothane (2). We, therefore, required a shorter duration of anesthesia (32 min) than that employed by Dr. Nakatsu (300 min).

Our data show that for the study duration we employed, theophylline elimination was not significantly different between dogs anesthetized with halothane or enflurane, nor did elimination in awake, unanesthetized animals differ from that in those animals receiving either inhalation agent. Thus, our conclusion that "differences in arrhythmogenicity between enflurane and halothane after aminophylline administration are not related to alterations in theophylline pharmacokinetics" (1) still appears valid.

We note that when Dr. Nakatsu recalculated his halothane data using sampling times similar to ours, halothane elimination half-life was 105 min, "close to the values reported by Berger et al." (72 min). In addition, Dr. Nakatsu reports a theophylline half-life of 283 min in his control animals not receiving inhalation anesthetic, similar to the 216 min found in our control group.

We would conclude that differences between Dr. Nakatsu's study and ours are more in interpretation than in fact. He might reach our conclusions given our data; we might reach his given his. We hope his group will see fit to publish a more detailed account of their findings so that any important variations in our experimental protocols might be determined. For example, anesthetic concentration would seem critical in these pharmacokinetic studies: we reported peak end-tidal halothane concentrations of 0.76–0.78 ± 0.02% (mean ± SEM) in our intubated animals, whereas Dr. Nakatsu notes only that "Halothane . . . [was] administered at between 1 and 2% to provide the depth of anesthesia required for our experiments." Such differences might go far toward reconciling our disparate conclusions.

Jack M. Berger, MD, PhD
Maxicare Medical Center
Department of Surgery
5525 West Slauson Avenue
Los Angeles, CA 90056

Joseph A. Stirt, MD
Department of Anesthesiology, Box 238
University of Virginia Medical Center
Charlottesville, VA 22908

Stuart F. Sullivan, MD
Department of Anesthesiology
UCLA School of Medicine
Los Angeles, CA 90024

References

1. Berger JM, Stirt JA, Sullivan SF. Enflurane, halothane, and aminophylline-uptake and pharmacokinetics. Anesth Analg 1983;62:733–7.
2. Stirt JA, Berger JM, Roe SD, Ricker SM, Sullivan SF. Halothane-induced cardiac arrhythmias following administration of aminophylline in experimental animals. Anesth Analg 1981;60:517–20.

A Complication Caused by an Adhesive Plastic Drape

To the Editor:

We describe a unique case of tension pneumothorax during anesthesia. Seven days before surgery the 78-yr old patient developed severe dyspnea that chest roentgenograms showed to be due to a large left pneumothorax. A chest tube was inserted and resulted in reexpansion of the left lung and relief of symptoms. The patient had a long history of cigarette smoking and severe chronic obstructive pulmonary disease (FEV = 860 ml). The diagnosis was spontaneous pneumothorax due to ruptured blebs. When the blebs failed to seal, the patient was scheduled for resection of the blebs and pleurodesis.

He was brought to the operating room breathing comfortably with a left chest tube in place. Anesthesia was induced during spontaneous ventilation with halothane in oxygen. After adequate anesthesia was obtained, the trachea was intubated and controlled ventilation was begun. After the uneventful induction and before surgical cleansing of the operative site, the surgeon removed the chest tube. During this and during initial application of surgical drapes the patient's blood pressure remained stable at 120/80 mm Hg, despite positive pressure ventilation. At the conclusion of draping, approximately 2 min after an adhesive plastic drape was placed over the operative site and chest tube wound, the patient's blood pressure precipitously decreased to 50/10 mm Hg. The surgeon was informed and within 2 min opened the chest. Less than 1 min after opening the chest, the blood pressure returned to 120/80 mm Hg. Surgery proceeded without further incident.

We believe this sequence of events can be explained in the following manner. Although the chest tube was removed during positive pressure ventilation, the 7-day-old chest tube wound remained patent and prevented the development of a tension pneumothorax, thus accounting for the absence of difficulties during that period. However, when the plastic adhesive drape was placed over the wound it effectively produced an airtight left hemithorax and caused the rapid onset of a tension pneumothorax that resulted in the sudden hypotension. When the chest was opened, the pneumothorax was relieved and the blood pressure returned rapidly to its previous level. The diagnostic whoosh of air was not heard when the chest was opened, possibly because of our very gentle ventilation at the time or because the incision created a sudden 8-cm wound that may have been large enough to relieve the gas pressure without creating an audible rush of air. The whoosh, although sufficient, is not necessary to diagnose tension pneumothorax. The sequence and close timing of the events leave us no other plausible explanation for the sudden hypotension and its equally sudden return to normal after the opening of the chest. Although seldom a problem, one should bear in mind that the plastic adhesive drapes commonly used during surgical procedures can create a sudden liquid- or gas-tight seal.

Robert Litwack, MD
Denis Bourke, MD
Department of Anesthesiology
University Hospital
Boston, MA 02118

Hypocarbia and Myocardial Circulation

To the Editor:

I read the paper by Coetzee et al. (1) with great pleasure and interest. Essentially, the investigators have demonstrated that hypocarbia can be accompanied by a decrease in myocardial blood flow with no changes in myocardial function or any signs of myocardial ischemia. The maintenance of normal regional myocardial function during hypocarbia is attributed to baseline myocardial overperfusion in the model that the author used. This might very well be true; however, I would like to offer an alternative explanation.

It has been demonstrated that 9-μm spheres provide a reliable estimate of nutritive blood flow whereas 15-μm spheres reflect total (nutritive and nonnutritive) blood flow (2,3). We have recently completed a study on regional blood flow during hypocarbia in monkeys using a pair of differently sized microsphere sets—15 and 9 μm in diameter (4). The results showed that total myocardial blood flow (through nutritive and nonnutritive vessels) determined with 15-μm spheres significantly decreased during hypocarbia (Pa_{CO_2} = 28 ± 1.8 mm Hg) by 31% (from 2.25 ± 0.60 to 1.54 ± 0.25 $ml \cdot min^{-1} \cdot g^{-1}$), whereas myocardial blood flow determined by 9-μm spheres did not change significantly. Thus, the fragment of our data gathered using 15-μm spheres agrees with the results achieved by Coetzee et al. (1) and many other investigators, showing a significant decrease in total coronary blood flow during hypocarbia. It seems, however, that the use of a pair of differently sized microsphere sets has provided additional information that could not be obtained with only 15-μm spheres or electromagnetic flowmeters: namely, that measured with 9-μm spheres nutritive coronary blood flow, which is obviously more important for myocardial function than nonnutritive flow, was well perserved during hypocarbia.

These data might mean that hypocarbia is not as dangerous for myocardial circulation and function as we are accustomed to think.

Simon Gelman, MD, PhD
Department of Anesthesiology
School of Medicine
The University of Alabama in Birmingham
Birmingham, AL 35294

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Book Reviews

Quality of Care in Anaesthetic Practice

John N. Lunn, ed and foreword by G.E. Hale Enderby. London: Macmillan Press, 1984, 314 pp. $12.50.

It is difficult to think of a more timely subject than quality of care in anesthetic practice, covered in this multiauthored text edited by John M. Lunn and published jointly by the Royal Society of Medicine and the Macmillan Press. One only needs to consider the current importance of such factors as the medical malpractice dilemma, the new standards of The Joint Commission on Accreditation of Hospitals, consumerism, the efforts of physicians to develop valid quality assurance programs, and such exploitative journalism as the television show, "20/20" which featured, with excessive editorial license, some horrendous anesthetic misadventures. Quality of medical care is the centerpiece of such issues.

Of the 50 contributors to this published symposium, 47 are from the United Kingdom and three are from the United States. While this might, at first glance, suggest that the material covered is more aptly pertinent to the British than to the American scene, the differences between the two countries do not significantly detract from the commonality of the issues involved. Where such differences do occur, it is a question of degree rather than direction.

In the preface, Dr. Lunn states that the 13 chapters, "have been subjected to more peer review than most chapters in multiauthored books." This happy circumstance results from a conference at which the chapters and commentaries in this book were presented by the individual contributors.

While refraining from reciting the title of each chapter, a sense of this work may be derived from listing the subjects generally covered: quality assurance, anesthetic morbidity and mortality, and the interrelationship of such issues as diverse as continuing medical education, departmental organization, career counseling, resident selection, evaluation of training, and leadership. At firsthand, this grouping appears to be a mixed bag.

Despite, however, the difference in readability and style that one expects in a multiauthored text, a thread of continuity exists throughout. The very diversity of the subjects covered emphasize the multiplicity of factors associated with our perceptions of quality. An additional plus for this approach to a difficult subject are the commentaries that appear at the end of each formal presentation. The reader is thus able to match his or her own reaction to the topic, as presented, against the reactions of those who heard the original presentations.

The book is 314 pages long, has a useful subject index, and is a significant contribution to the literature dealing with our current preoccupations with quality assurance.

E.S. Siker, MD
Department of Anesthesiology
Mercy Hospital
Pittsburgh, PA

Current Concepts in Regional Anaesthesia

J.W. Van Kleef, MD, A.G.L. Burm, MD, J. Spierdijk, MD, eds. The Hague: Martinus Nijhoff Publishers, 1984, 252 pp, $46.50.

This book is an eclectic compilation of papers presented at the second general meeting of the European Society of Regional Anaesthesia. Authorship is divided between European and American contributors. Subjects covered run the gamut from surgical anesthetic techniques to obstetric physiology to acute and chronic pain therapy. The volume is without theme except for the sometimes thin thread of orientation to regional anesthesia. There is no sense of editorial command, and therefore writing style, illustrations, and reference lists are highly variable. Some of the photographic reproductions of computed tomograms are so poor that anatomic features are obscured rather than elucidated.

A delightful aspect of this book is the creative and sometimes imaginative descriptions of certain nerve block techniques. Regional anesthesia will always be an art form, but increasingly we see attempts to investigate it in a scientific mode. This is good albeit often frustrating. Anatomy is not always consistent from patient to patient, and local anesthetic drug responses are also highly individualistic. Each book must be "baked" separately. However, I salute any attempt to popularize this oft neglected aspect of the practice of anesthesia. This book helps achieve that goal.

Gale E. Thompson, MD
Department of Anesthesiology
The Mason Clinic
Seattle, WA 98111

Books Received

The Year Book of Critical Care Medicine 1984. Mark C. Rogers, Frank V. McLean Booth, et al. Chicago: Year Book Medical Publishers, 1984, 462 pp, $39.95.

Life Support Systems in Intensive Care. Robert H. Bartlett, Walter M. Whitehouse Jr, Jeremiah G. Turcotte. Chicago: Year Book Medical Publishers, 1984, 615 pp, $49.95.

Manual of Cardiac Anesthesia. Stephen J. Thomas. New York: Churchill Livingstone, 1984, 469 pp, $27.50.

A Guide for Authors

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Nicholas M. Greene, MD
Editor in Chief
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- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
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2. *Corporate Author*
   The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977;2:242–4.
3. *No Author Given*
   Anonymous. Coffee drinking and cancer of the pancreas (Editorial). Br Med J 1981;283:628.
4. *Journal Supplement*
   Mastri AR. Neuropathy of diabetic neurogenic bladder. Ann Intern Med 1980;92(2 Pt 2):316–8.

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Books and Other Monographs:

6. *Personal Author(s)*
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   DuPont B. Bone marrow transplantation in severe combined immunodeficiency with an unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974:44–6.
10. *Monograph in a Series*
    Hunninghake GW, Gadek JE, Szapiel SV, et al. The human alveolar macrophage. In: Harris CC, ed. Cultured human cells and tissues in biomedical research. New York: Academic Press, 1980:54–6. (Stoner GD, ed. Methods and perspectives in cell biology; vol. 1).
11. *Agency Publication*
    Ranofsky AL. Surgical operations in short-stay hospitals: United States—1975. Hyattsville, Maryland: National Center for Health Statistics, 1978; DHEW publication no. (PHS) 78–1785. (Vital and health statistics; series 13; no. 34).
12. *Dissertation or Thesis*
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ATIVAN® (LORAZEPAM) CIV
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

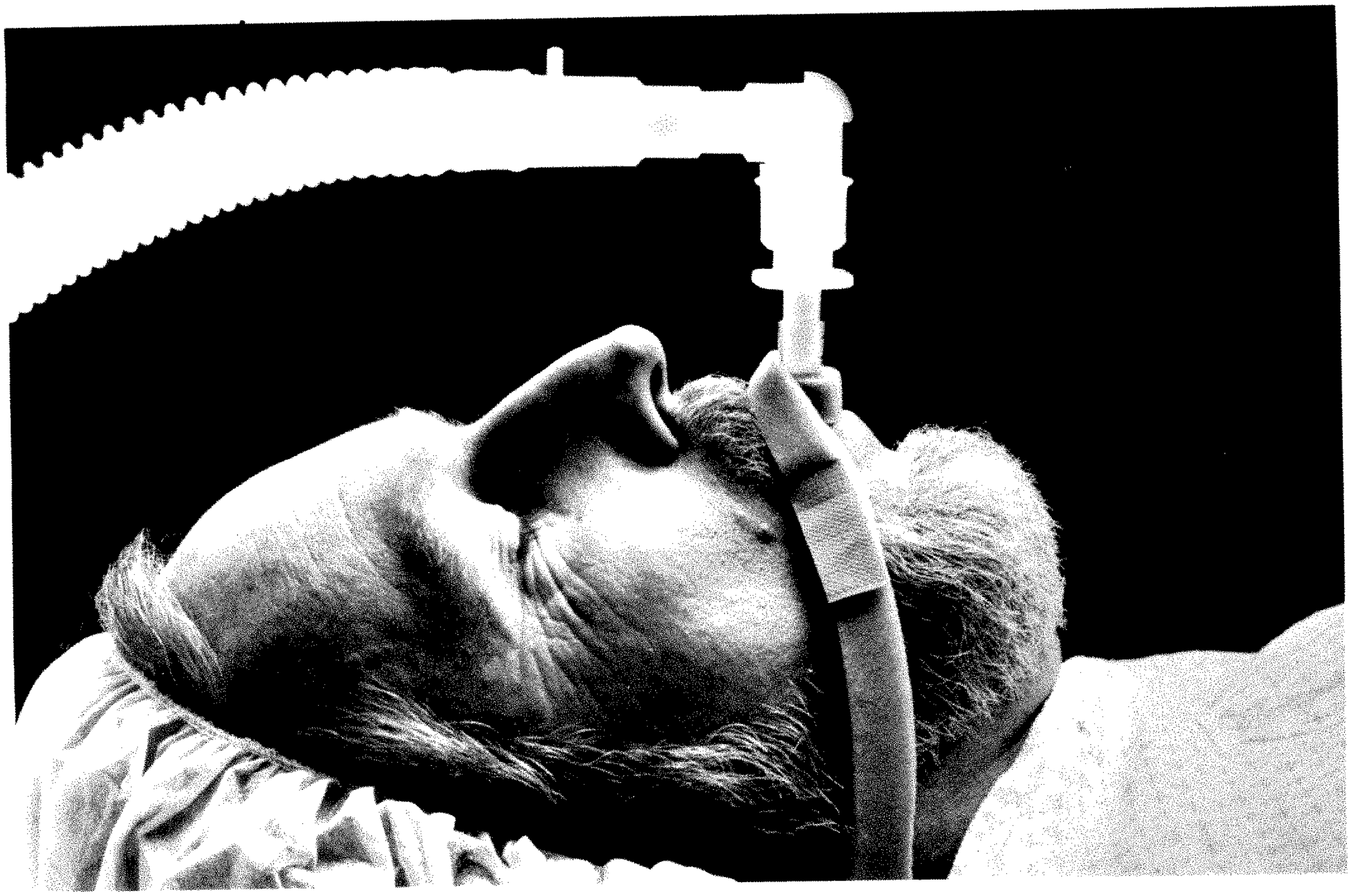
For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101
TM

CI 3117-1 7/31/80



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While others slip and slide all over the place, we've made a name for ourselves by staying put.

No more fumbling for the tape. No more sticky adhesive devices. And no more concerns for the security and safety of your patient's airway. Now enjoy the speed, simplicity and protection of STRAPEZE.

Strap versus tape

Tape kinks, binds, and often loses its adhesive qualities under operating conditions. STRAPEZE, as its name implies, is a strap made of 100% non-allergenic Velfoam II®, a very durable and lightweight material with a foam core sandwiched between outer layers of soft, synthetic lambs-wool.

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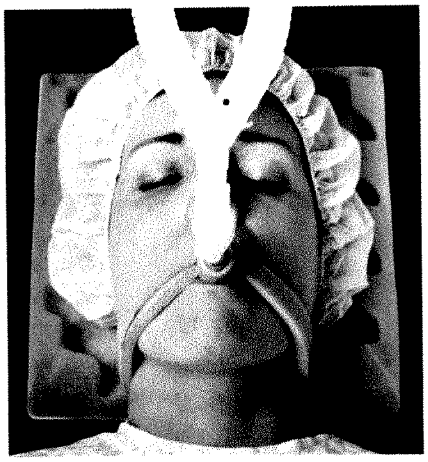
The STRAPEZE "one-step" fastening concept brings a new measure of assurance and security to endotracheal tube placement. And there's nothing else like it for ease of use. You simply attach one end of STRAPEZE to the tube, slip the strap behind the patient's neck, loop around tube and fasten with the Velcro tab back onto the strap's velvety surface. Job finished!



Stays put—or it's not STRAPEZE!

Now you can forget about accidental extubations or bronchial intubations. STRAPEZE ensures precise and positive positioning of the tube. Where you put it, is where it stays. Which means the tube won't pull out, and it won't push down. Needless to say, such assurances can be a lifesaver.

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STRAPEZE was designed to answer the demanding needs of today's medical professional. Its innovative simplicity erases the tedium and uncertainty of performing an important task. And its specialized function is another example of ProTech Pacific's ongoing commitment to your profession. STRAPEZE. New convenience. New security. New comfort. And, for all these assurances, very inexpensive. For the comfort of the intubated patient, STRAPEZE is here to stay. Because it *stays put.*

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1984 (58th Congress) Review Course Lectures—$6.00.

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Prevent pain.
Prolong analgesia.
Promote early ambulation.

PRESERVATIVE-FREE

Duramorph® PF

(morphine sulfate injection, USP) C II

creates new options in pain management

1 DURAMORPH® PF provides profound site-selective analgesia.

DURAMORPH® PF delivers preservative-free morphine directly to localized opiate receptors in the spinal cord, selectively blocking nociceptive impulse transmission to the brain's pain centers.

2 DURAMORPH® PF prevents postoperative pain when administered at the completion of surgery.

A single 5 mg epidural injection before the onset of postoperative pain provides pain relief associated with many obstetric/gynecologic, orthopedic, thoracic, and abdominal procedures. Use of DURAMORPH® PF is particularly convenient when an epidural catheter is already in place for operative anesthesia.

"From a humanitarian viewpoint, epidural morphine could be considered the ideal postoperative analgesic . . ." [1]

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Guidelines for Administration of DURAMORPH® PF

- The epidural route should be used whenever possible; intrathecal administration has been associated with greater potential for immediate or delayed adverse effects.
- Administration should be limited to the lumbar region whenever possible; thoracic injection has been shown to dramatically increase the incidence of respiratory depression.
- Predisposing factors in morphine-related respiratory depression include: thoracic administration,[4] advanced age,[4] reduced ventilatory capacity,[5] high doses,[6] concomitant administration of opioids,[5] supine body position,[7] CNS depressants,[5] and raised intrathoracic pressure.[8] Careful selection of patients, avoidance of opiate premedication, and maintenance of patients in a head-up position may minimize the occurrence of respiratory depression.

See complete prescribing information

3

DURAMORPH® PF relieves pain for up to 24 hours with a single epidural injection.

DURAMORPH® PF provides extended pain protection with a duration of analgesic effect that is nearly four times longer than that of conventional systemic narcotics (IV morphine).[1]

4

DURAMORPH® PF is associated with a low incidence of respiratory depression.

Delayed respiratory depression has been reported; patient monitoring should be continued for at least 24 hours after each dose. Naloxone reverses respiratory depression without diminishing analgesia.

5

DURAMORPH® PF maintains patient comfort with virtually no sedation, or loss of motor or sympathetic function.

DURAMORPH® PF out-performs conventional systemic narcotics and local anesthetics in producing site-selective analgesia. Patients are alert and more active participants in their nursing and rehabilitative care.

6

DURAMORPH® PF promotes early ambulation and reduces postoperative complications.

Patients receiving DURAMORPH® PF frequently become ambulatory earlier than patients receiving conventional systemic narcotics—often in as little as half the time[1]—which may reduce the risk of postoperative respiratory and thromboembolic complications.[3]

> ***"Due to absence of sedation and the lack of orthostatic hypotension, high risk patients . . . ambulate early leading to decreased risk for postoperative thromboembolic and respiratory complications."***[2]

7

DURAMORPH® PF may hasten patient recovery and shorten hospital stays.

In a study of patients at high risk of postoperative complications, epidural morphine shortened hospital stays after elective gastroplasty from an average of 9 days to 7 days.[3]

8

DURAMORPH® PF may mean cost savings in postoperative care.

The benefits of early ambulation, greater patient cooperation with nursing/rehabilitative care, fewer postoperative complications, and shortened hospital stays—offset against the moderately increased costs of short-term postoperative monitoring—may result in a significant net savings in the costs of medical care, an important consideration for institutions dependent on fixed-cost reimbursement policies.

> ***"... effective analgesia, early ambulation, early normalization of gastrointestinal function, and minimal respiratory complications in the postoperative period all contributed to a shorter hospitalization time in patients receiving epidural morphine analgesia."***[3]

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PRESERVATIVE-FREE

Duramorph® PF

(morphine sulfate injection, USP) C II

DESCRIPTION

Preservative-free DURAMORPH® PF (Morphine Sulfate Injection, USP) is a sterile, pyrogen-free, isobaric solution free of antioxidants, preservatives or other potentially neurotoxic additives, and is intended for intravenous, epidural or intrathecal administration as a narcotic analgesic. Each milliliter contains morphine sulfate 0.5 mg or 1 mg (Warning: May Be Habit Forming) and sodium chloride 9 mg in Water for Injection. pH range is 2.5-6.0. Ampuls are sealed under nitrogen. Each Dosette® ampul is intended for SINGLE USE ONLY. Discard any unused portion. DO NOT AUTOCLAVE.

INDICATIONS AND USAGE

Preservative-free DURAMORPH® PF is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

CONTRAINDICATIONS

DURAMORPH® PF is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

WARNINGS

DURAMORPH® PF administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.

FACILITIES WHERE DURAMORPH® PF IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.

SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.

Morphine sulfate may be habit forming. (See Drug Abuse and Dependence section.)

PRECAUTIONS

GENERAL

Preservative-free DURAMORPH® PF (Morphine Sulfate Injection, USP) should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial/intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis).

Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

It is recommended that administration of DURAMORPH® PF by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to risks inherent in urethral catheterization, e.g., sepsis, when epidural or intrathecal administration is considered, especially in the perioperative period.

Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

DRUG INTERACTIONS

Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY

Teratogenic effects—Pregnancy Category C. Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.

Nonteratogenic effects. Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

LABOR AND DELIVERY

Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

Epidurally and intrathecally administered morphine readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that *epidural* administration has little or no effect on the relief of labor pain.

However, studies have suggested that in most cases 0.2 to 1 mg of morphine *intrathecally* provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr, for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

NURSING MOTHERS

Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most serious side effect is respiratory depression. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (See Warnings and Overdosage sections). Even without clinical evidence of ventilatory inadequacy, a diminished CO_2 ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.

Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10-20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see Precautions). Pruritus, nausea/vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).

Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see Drug Abuse and Dependence section).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as uticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Morphine sulfate is a Schedule II substance under the Drug Enforcement Administration classification.

Abuse: Morphine has recognized abuse potential.

Dependence: Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Nonteratogenic effects under Pregnancy.)

OVERDOSAGE

Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, simultaneously with respiratory resuscitation. *As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary.* Patients should be closely observed for evidence of renarcotization. *Note: Respiratory depression may be delayed in onset up to 24 hours* following epidural or intrathecal administration. In painful conditions, reversal of narcotic effect may result in acute onset of pain and release of catecholamines. Careful administration of naloxone may permit reversal of side effects without affecting analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

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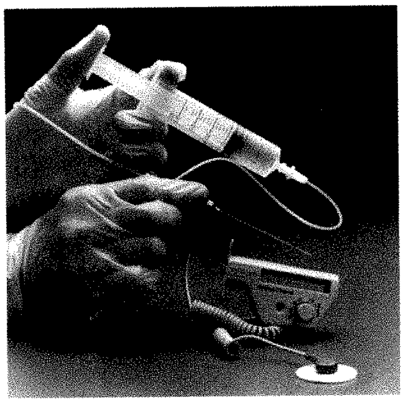

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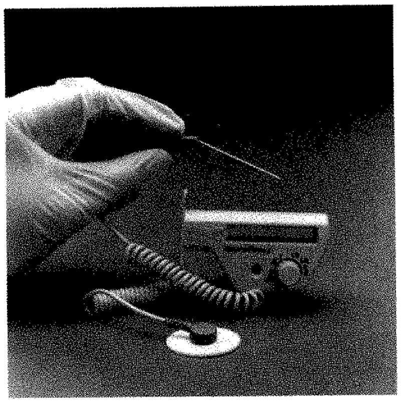

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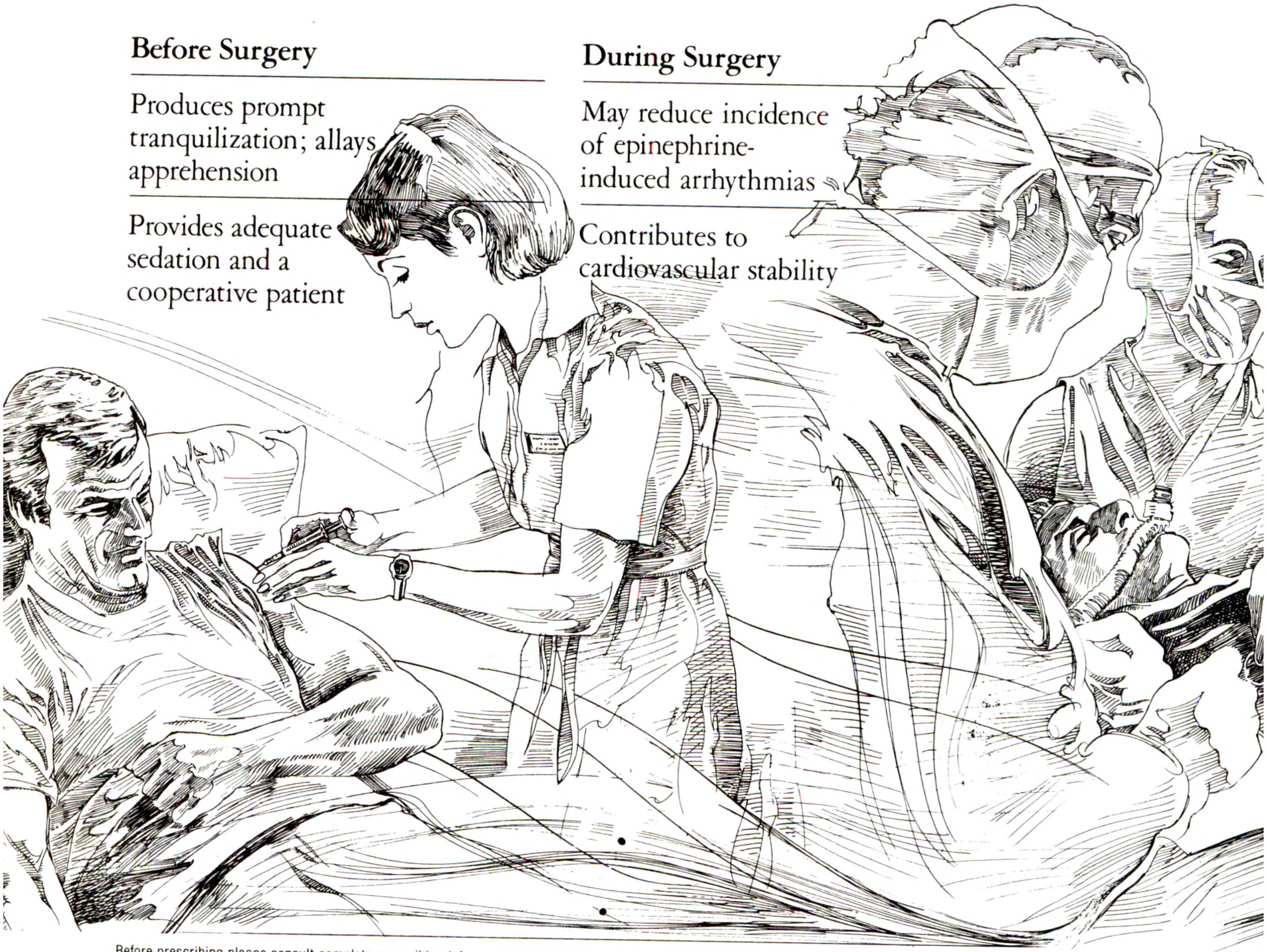

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CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spina and peridural anesthesia, tilting the patient into a head dow position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Car should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do n correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinepl rine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary art rial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs shou be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

goes on helping... postoperative period

After Surgery

Exerts potent antiemetic effect

Reduces need for postoperative narcotics

Inapsine® (droperidol) Injection

The premedication that does more than premedicate

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of
APSINE (droperidol). Restlessness, hyperactivity, and anxi-
vhich can be either the result of inadequate dosage of
'INE (droperidol) or a part of the symptom complex of
'a may occur. When extrapyramidal symptoms occur,
usually be controlled with anti-parkinson agents.
.dverse reactions that have been reported are dizzi-
: and/or shivering, laryngospasm, bronchospasm
erative hallucinatory episodes (sometimes asso-
transient periods of mental depression).
PSINE (droperidol) is used with a narcotic anal-
s SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur.

Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR® injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: 2 ml. and 5 ml. ampoules—packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980
*See full prescribing information for complete description.
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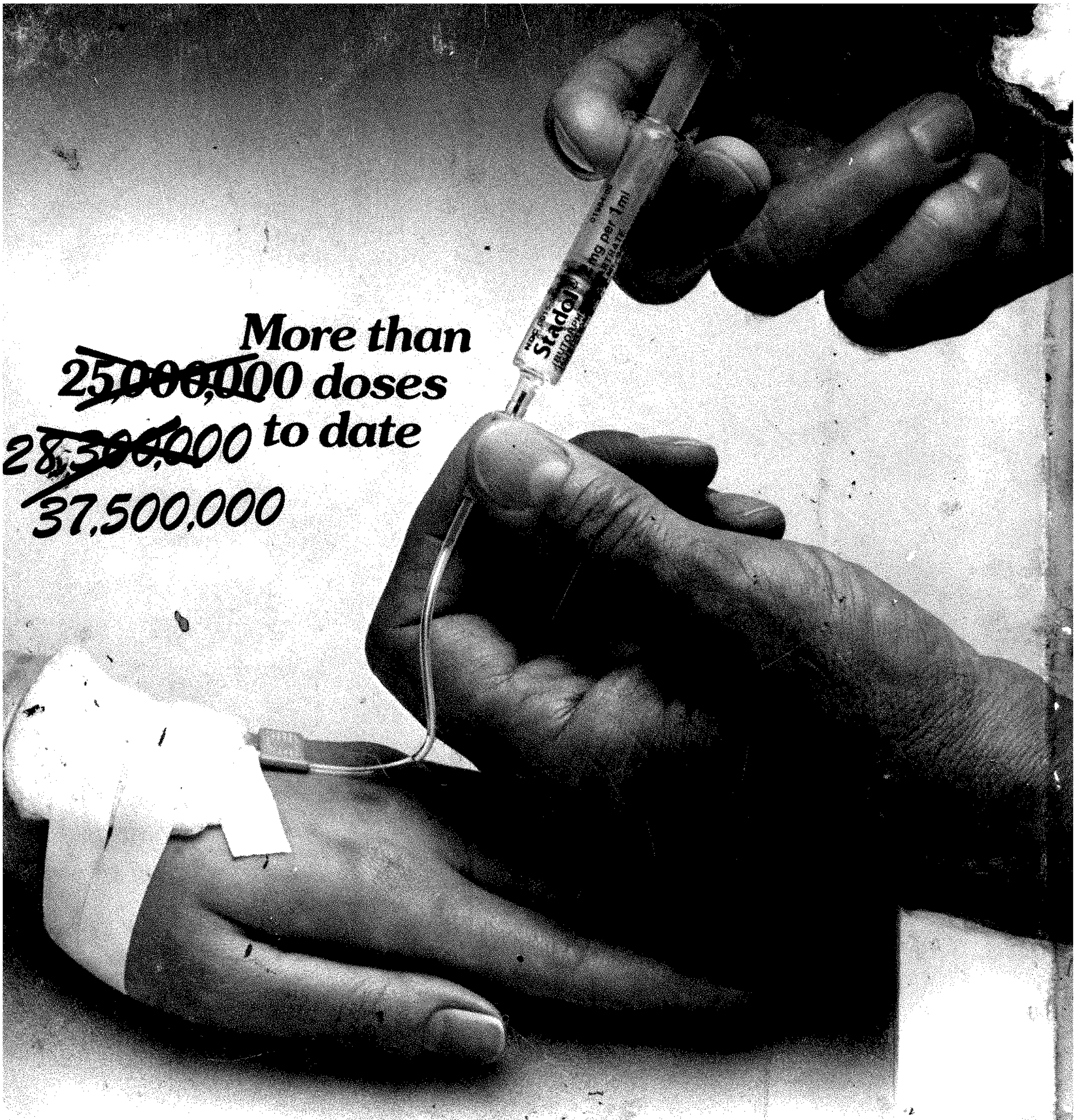
Janssen Pharmaceutica Inc. 501 George St., New Brunswick, N.J. 08903



HOSPITAL-PROVEN

Stadol® IM IV
(butorphanol tartrate)

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